Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Sentynl
2. **Company summary of information for patients (SIP)** from Sentynl
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Metabolic Support UK
   b. Willink Unit, Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust
5. **External Assessment Report** prepared by PenTAG
6. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company:**
   a. Main response
   b. Updated cost-effectiveness results
   c. Updated PSA results (corrected)
8. **Technical engagement responses from stakeholders:**
   a. Metabolic Support UK
   b. Willink Unit, Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust
9. **Technical engagement responses and statements from experts:**
   a. Dr Bernd Schwahn, Consultant Clinical Paediatrician in Inherited Metabolic Medicine – clinical expert, nominated by Metabolic Support UK
   b. Lucy Durrant, Parent – patient expert, nominated by Metabolic Support UK

10. **External Assessment Report critique of company response to technical engagement** prepared by PenTAG**:**
    a. Main critique
    b. Updated cost-effectiveness results

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Document B

Company evidence submission

April 2024

File name	Version	Contains confidential information	Date
Form B	**V3**	**Yes**	**10/05/2024**

Abbreviations list

AE	Adverse events
AED	Anti-epileptic drugs
ATE	Average treatment effect
BL	Baseline
BMI	Body mass index
BSC	Best supportive care
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
CP	Cerebral palsy
CRF	Case report form
CSR	Clinical study reports
DS	Dravet syndrome
EMA	European Medicines Agency
FAS	Full analysis set
FUP	Follow-up
GA	Gestational age
GABA	γ-aminobutyric acid
GMAS	Genotype-matched analysis set
GMFCS	Gross Motor Function Classification System
GTP	Guanosine triphosphate
HIE	Hypoxic-ischaemic encephalopathy
ISE	Integrated Summary of Efficacy
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MoCD	Molybdenum cofactor deficiency
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PD	Pharmacodynamics
PEDI	Paediatric Evaluation of Disability Inventory
PFAS	Prospective full analysis set
PK	Pharmacokinetics
PT	Preferred term
RSV	Respiratory syncytial virus
SAE	Serious adverse events
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SOX	Sulphite oxidase
SSC	S-sulphocysteine
TEAE	Treatment-emergent adverse events
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, which is 'for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A'.(1) The decision problem addressed by this submission is defined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with MoCD Type A	People with MoCD Type A	Not applicable
Intervention	Fosdenopterin (Nulibry®)	Fosdenopterin (Nulibry®)	Not applicable
Comparator(s)	Established clinical management without fosdenopterin	Established clinical management without fosdenopterin	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival • Cognitive function • Gross motor function • Adverse effects of treatment • Body weight and nutritional parameters (including growth and development) • Neurological development parameters • Frequency of seizures • Mortality • Severity of disease	The outcomes measured considered in the submission are: • Overall survival • Cognitive function • Gross motor function • Adverse effects of treatment • Body weight and nutritional parameters (including growth and development) • Neurological development parameters • Frequency of seizures • Mortality • Severity of disease	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life (for patients and carers)	• Health-related quality of life (for patients and carers)	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.	A cost-utility analysis will be presented, as per the reference case. The cost-effectiveness of fosdenopterin compared with standard of care will be expressed in terms of incremental cost per quality-adjusted life year. The time horizon will cover the entire lifetime horizon, as fosdenopterin is a life-extending therapy. Costs will be considered from an NHS and Personal Social Services perspective. Any commercial arrangements will be included in the analysis.	Not applicable
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	In line with NICE scope.	Not applicable

B.1.2 Description of the technology being evaluated

The technology being evaluated is fosdenopterin (Nulibry®), a substrate replacement therapy which addresses the underlying cause of MoCD Type A. A summary of the technology is provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	• Approved name: Fosdenopterin • Brand name: Nulibry®
Mechanism of action	Patients with MoCD Type A have mutations in the molybdenum cofactor synthesis 1 (*MOCS1*) gene leading to deficient MOCS1A/B dependent synthesis of the intermediate substrate, cPMP. Substrate replacement therapy with fosdenopterin 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.
Marketing authorisation/CE mark status	Fosdenopterin was given orphan designation by the European Medicines Agency (EMA) on 20th September 2010 (EU/3/10/777) and was approved by the EMA under exceptional circumstances in September 2022, making it the first medicine approved in Europe to treat patients with MoCD Type A. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	EMA: 'Fosdenopterin is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.' [redacted]'
Method of administration and dosage	Fosdenopterin is for intravenous use only. Fosdenopterin is intended for administration at an infusion rate of 1.5 mL/min after reconstitution with 5 mL of sterile water for injection. Dose volumes below 2 mL may require syringe administration by slow intravenous push. If deemed appropriate by a healthcare professional, fosdenopterin may be administered at home by the patient's caregiver. If fosdenopterin is administered by a caregiver/patient, the caregiver/patient must read and follow carefully the detailed "instructions for the user" on the preparation, administration, storage, and disposal of fosdenopterin provided in the carton. The healthcare professional should calculate and provide the volume of fosdenopterin in millilitres (mL) and the number of vials needed for each dose to the caregiver/patient. In patients less than 1 year of age, the recommended dose of fosdenopterin is titrated based on gestational age. For patients less than 1 year of age who are preterm neonates (gestational age <37 weeks), the recommended

<table>
<tr><td>UK approved name and brand name</td><td>Approved name: Fosdenopterin
Brand name: Nulibry®</td></tr>
<tr><td></td><td>starting dose of fosdenopterin is 0.40 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months, as shown in Table 3.
For patients less than 1 year of age who are term neonates (gestational age ≥37 weeks), the recommended starting dose of fosdenopterin is 0.55 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months, as shown in Table 3.
For the paediatric population from 1 year to less than 18 years of age and adults, the recommended dose of fosdenopterin is 0.90 mg/kg (based on actual body weight) administered intravenously once daily.
Table 3: Starting dose and titration schedule of fosdenopterin for patients less than 1 year of age by gestational age
<table>
<tr><th>Titration schedule</th><th>Preterm neonate (gestational age <37 weeks)</th><th>Term neonates (gestational age ≥37 weeks)</th></tr>
<tr><td>Initial dose</td><td>0.40 mg/kg once daily</td><td>0.55 mg/kg once daily</td></tr>
<tr><td>Dose at Month 1</td><td>0.70 mg/kg once daily</td><td>0.75 mg/kg once daily</td></tr>
<tr><td>Dose at Month 3</td><td>0.90 mg/kg once daily</td><td>0.90 mg/kg once daily</td></tr>
</table></td></tr>
<tr><td>Additional tests or investigations</td><td>Fosdenopterin is only to be administered if the patient has a confirmed genetic diagnosis or presumptive diagnosis of MoCD Type A.
Patients with a presumptive diagnosis of MoCD Type A need to have a genetic test to confirm the diagnosis of MoCD Type A. Fosdenopterin must be discontinued if the MoCD Type A diagnosis is not confirmed by genetic testing.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>Fosdenopterin is intended as a lifelong treatment for a chronic, severe, and life-threatening condition.
The list price of fosdenopterin is £1,205.51 per 9.5mg vial.
A vial of fosdenopterin contains 9.5mg of product. Dose administration is based on weight. Titration is based on the schedule outlined in the SmPC, and is reported in Table 3.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>Simple PAS of [redacted]</td></tr>
</table>

Abbreviations: cPMP=cyclic pyranopterin monophosphate; MoCD Type A=molybdenum cofactor deficiency type A; MOCS1=molybdenum cofactor synthesis 1; MHRA=Medicines and Healthcare products Regulatory Agency; SOX=sulphite oxidase; SmPC=summary of product characteristics; WHO=World Health Organisation.

B.1.3 Health condition and position of the technology in the treatment pathway

Summary

Pathophysiology

- MoCD is a rare, genetic inborn error of metabolism impacting molybdenum cofactor (MoCo) synthesis, crucial for preventing toxic sulphite accumulation in the brain.(2-7)
- *MOCS1* gene mutations cause MoCD Type A, hindering the conversion of guanosine triphosphate (GTP) to cPMP.(2, 8) Reduced sulphite oxidase activity due to MoCo deficiency allows toxic sulphite accumulation, leading to irreversible neuronal damage. (3, 7, 9)

Epidemiology

- Globally, around 100 MoCD cases have been reported, with Type A prevailing. This presents challenges in estimating incidence; the most recent estimation, based on the Hardy-Weinberg equation and allelic frequencies of represented variants was within the range of one in 341,690 to 411,187.(10) To the company's knowledge, there is one living case of MoCD Type A in England.

Symptoms

- MoCD symptoms typically manifest shortly after birth or during infancy, with a systematic review reporting that 73% of cases present within the first 28 days of life. In a natural history study, MoCD Type A patients commonly exhibited seizures (93%) and feeding difficulties (85.4%) as initial signs.(9)
- Severe brain damage, reflected in characteristic magnetic resonance imaging (MRI) patterns, leads to psychomotor impairment, hindering coordinated movements and communication. Patients often develop sequelae, including limb hypertonicity (87.8%), developmental delay (85.4%), and truncal hypotonia (70.7%).(9)

Morbidity and mortality

- MoCD Type A's rapid and irreversible neurodegeneration results in severe clinical manifestations; without treatment, MoCD Type A patients usually do not survive beyond the first years of life, with a median survival of 4.23 years reported in a multinational study.(3, 9, 11, 12)
- This impacts caregivers as patients struggle with basic functions. Caregivers of rare diseases often face emotional and physical tolls, with high rates of anxiety and depression, and challenges in daily life, work, and social interactions.

Current treatments and unmet need

- No specific guidelines or licensed treatments for MoCD Type A exist, leaving best supportive care (BSC) as the standard, focusing on symptom relief rather than addressing the underlying cause.
- Current interventions, such as anti-epileptic drugs and low-sulphur diets, offer limited effectiveness in symptom control and overall prognosis improvement.
- A transformative treatment such as fosdenopterin is urgently needed to target the root cause of the disease, potentially enhancing seizure control, developmental outcomes, and overall survival rates, and thereby likely having a positive impact on the quality of life for patients and their families.

B.1.4 Disease overview

B.1.4.1 Pathophysiology

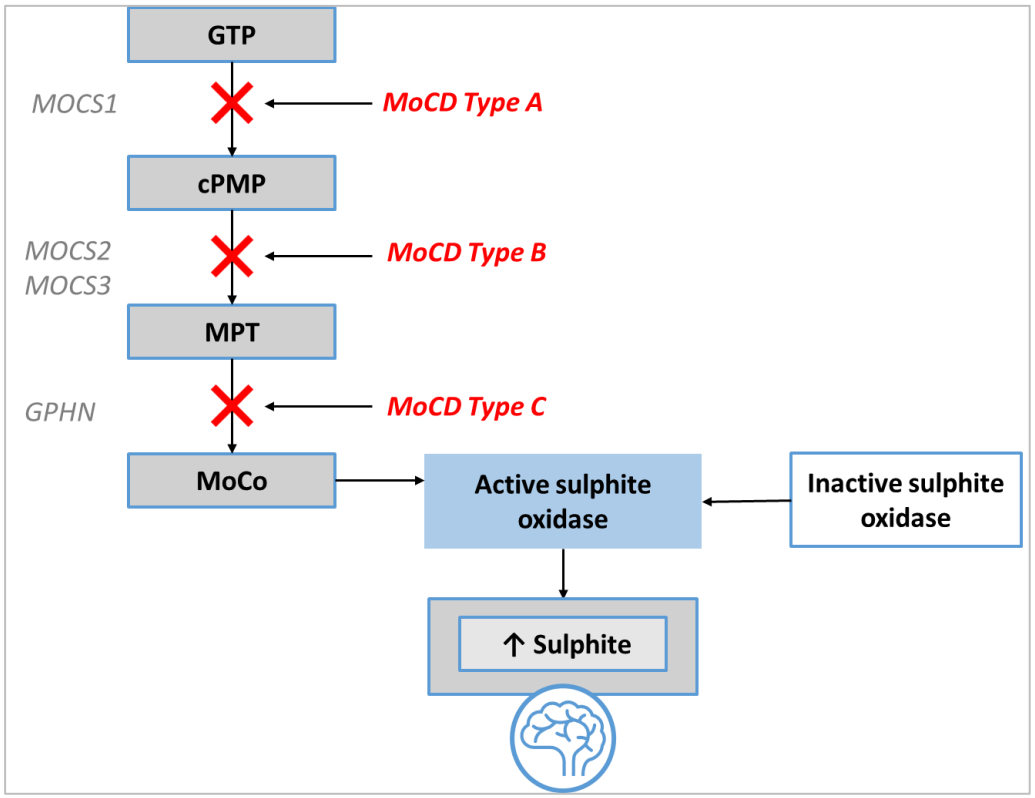
MoCD is a rare genetic inborn error of metabolism which affects the synthesis of MoCo necessary to prevent a toxic build-up of sulphite in the brain.(2-7) Please note that due to the rarity of the condition, literature from all subtypes of MoCD may be referenced throughout this document. These cases are denoted using the term 'MoCD'. However, in instances when 'MoCD Type A' is written in full, the literature addresses MoCD Type A specifically.

MoCD has three different types: Type A, Type B, and Type C. Type A is the most common form.(9) While each type is caused by a different genetic mutation in the MoCo synthesis pathway, they are clinically indistinguishable, as their pathophysiology primarily involves the accumulation of toxic metabolites, (e.g., sulphite).(9, 13)

MoCD Type A specifically arises from pathogenic variants in the *MOCS1* gene, which is responsible for the conversion of guanosine triphosphate (GTP) to cPMP.(14) In all subtypes of MoCD, there is a decrease in the production of MoCo, leading to a decrease in MoCo-dependent enzyme activity; this enzyme is sulphite oxidase.(2, 8)

Sulphite oxidase plays a critical role in preventing the build-up of toxic sulphite in the mitochondrial intermembrane space, converting it into non-toxic sulphate.(8, 13) It is this build-up of toxic sulphite which causes irreversible neuron degeneration and brain damage, leading to the characteristic clinical features of MoCD and, in most cases, to an early death.(3, 7, 9, 15)

Figure 1: MoCo biosynthetic pathway and pathogenesis of MoCD (2)



Abbreviations: cPMP=cyclic pyranopterin monophosphate; *GPHN*=gephyrin gene; GTP=guanosine triphosphate; MoCD=molybdenum cofactor deficiency; MoCo=molybdenum cofactor; *MOCS1*=molybdenum cofactor synthesis 1 gene; *MOCS2*=molybdenum cofactor synthesis 2 gene; *MOCS3*=molybdenum cofactor synthesis 3 gene; MPT=molybdopterin

B.1.4.2 Epidemiology

To date, approximately 100 cases of MoCD have been reported in the literature,(9, 16) representing numerous ethnic groups, with a higher incidence in areas of high consanguinity.(6, 17-19) The most recent estimation, based on the Hardy-Weinberg equation and allelic frequencies of represented variants was within the range of one in 341,690 to 411,187.(10)

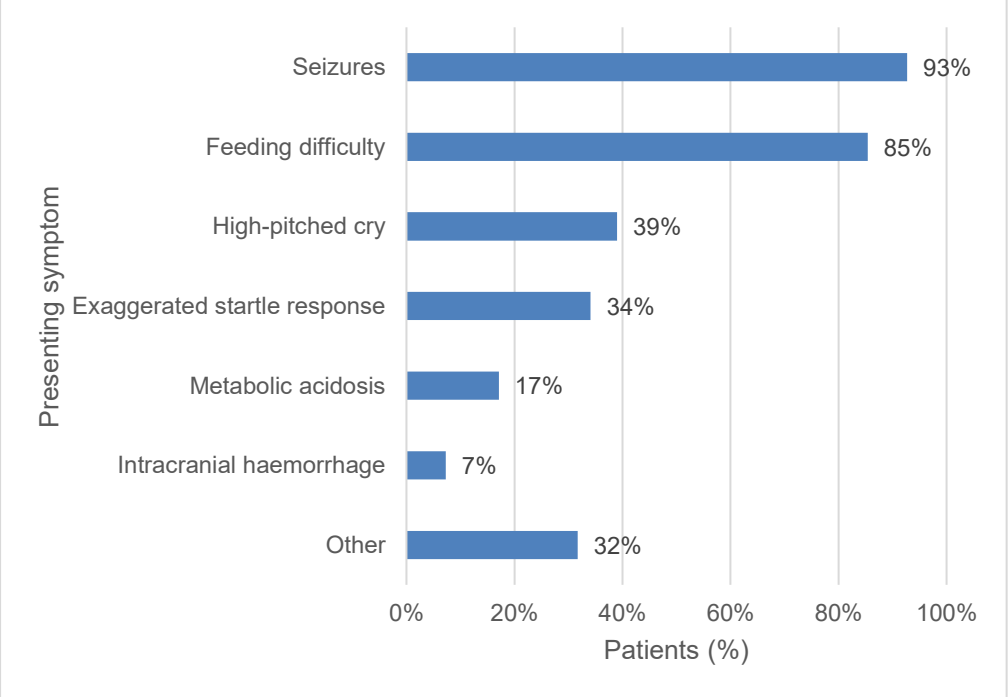
There is some evidence to suggest that MoCD Type A has been underdiagnosed due to a low awareness of the disease, which may have been compounded by the fact that until recently, a disease-modifying treatment was unavailable.(3, 20-24) Nevertheless, MoCD Type A remains an ultra-rare condition.

B.1.4.3 Symptoms

Symptoms typically present immediately after birth or during infancy.(7) In a systematic review of reported cases of MoCD (N=86, any type), 73% of patients presented symptoms within the first 28 days of life, and 46% presented symptoms on the first day of life.(7) The systematic review found that the presentation of MoCD can be variable. The most common initial signs or symptoms of MoCD were intractable seizures (72%), feeding difficulties (26%), and truncal hypotonia (11%).(7)

A noninterventional, observational, multinational, natural history study of patients with MoCD Type A (n=41) found the median age of onset of symptoms to be 2.0 days (range: 1-927).(9) The most common presenting signs were seizures (93%) and feeding difficulty (85.4%), as presented in Figure 2.(9)

Figure 2: Presenting symptoms of MoCD Type A patients in an international natural history study (n=41)



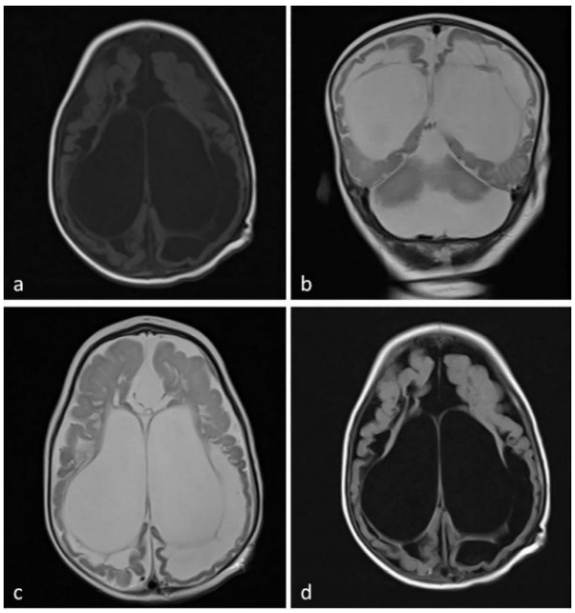
Source: Spiegel *et al.* (2022). Abbreviations: MoCD=molybdenum cofactor deficiency (9)

Patients with MoCD experience a severe clinical burden due to progressive brain damage. This is often observed via characteristic patterns on an MRI, including (25):

- Cystic encephalomalacia (damage, or loss of cortical tissue)

- Dysgenesis of the corpus callosum (incomplete development of the connective pathway in the brain)
- Abnormal white matter signal on the MRI
- Posterior fossa abnormalities (Mega cisterna magna, Dandy-Walker variant)
- Subcortical and periventricular white matter loss
- Ventriculomegaly (enlargement of the ventricles)

Figure 3: MRI of the brain of a patient with MoCD

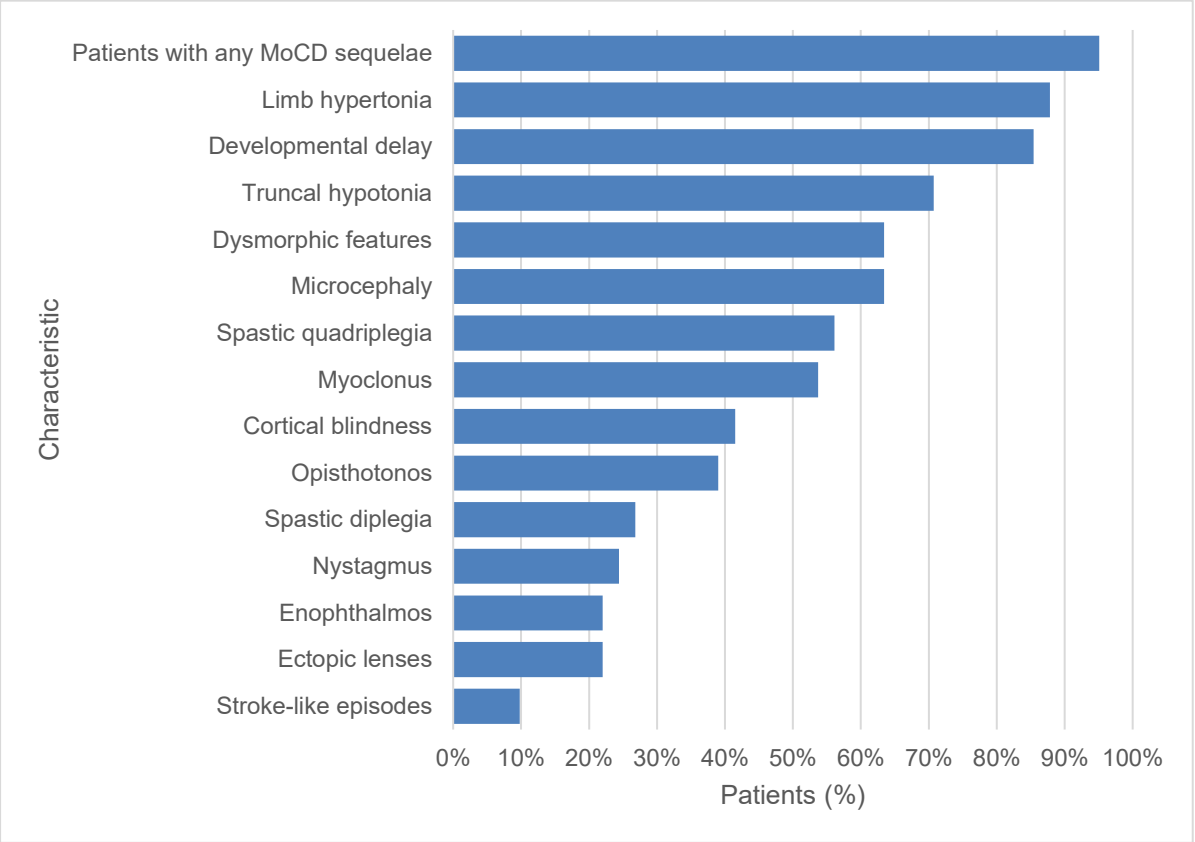


Source: Durmaz and Özbakır (2018). T1-weighted axial (a), T2-weighted coronal (b), T2-weighted axial (c), and axial fluid-attenuated inversion recovery sequence (d) in magnetic resonance images show ventriculomegaly, cystic encephalomalacia, and extensive subcortical and periventricular white matter loss and hyperintensity in white matter with atrophy (25).

This brain damage may lead to severe psychomotor impairment and an inability to make coordinated movements or communicate with the external environment.(15)

In a retrospective, international cohort of patients with MoCD Type A (N=41; date range NR), 92% of patients developed ≥1 disease sequela during follow-up, with the most common being limb hypertonicity (87.8%), developmental delay (85.4%), and truncal hypotonia (70.7%) (Figure 4).(9)

Figure 4: MoCD Type A sequelae for patients in an international natural history study (n=41)



Source: Spiegel *et al.* (2022). Abbreviations: MoCD=molybdenum cofactor deficiency (9).

Upon presentation of symptoms, patients suspected of having MoCD can be diagnosed by testing for changes in key biochemical markers such as elevated urine or plasma s-sulphocysteine (SSC), decreased or absent urine or plasma uric acid, or low plasma cysteine and homocysteine.(8, 12) Genetic testing is required to confirm the diagnosis of MoCD and subtype.(7)

Two forms of MoCD are currently recognised. The classical, severe form (early, or neonatal onset) appears in the first month of life. Intractable seizures, feeding difficulties, quadriplegia, and early death are common clinical findings.(26) Dysmorphic features are also described in most children with the classical form, most notably frontal bossing, full cheeks, widely spaced eyes, elongated palpebral fissures, thick lips, and long philtrum.(26)

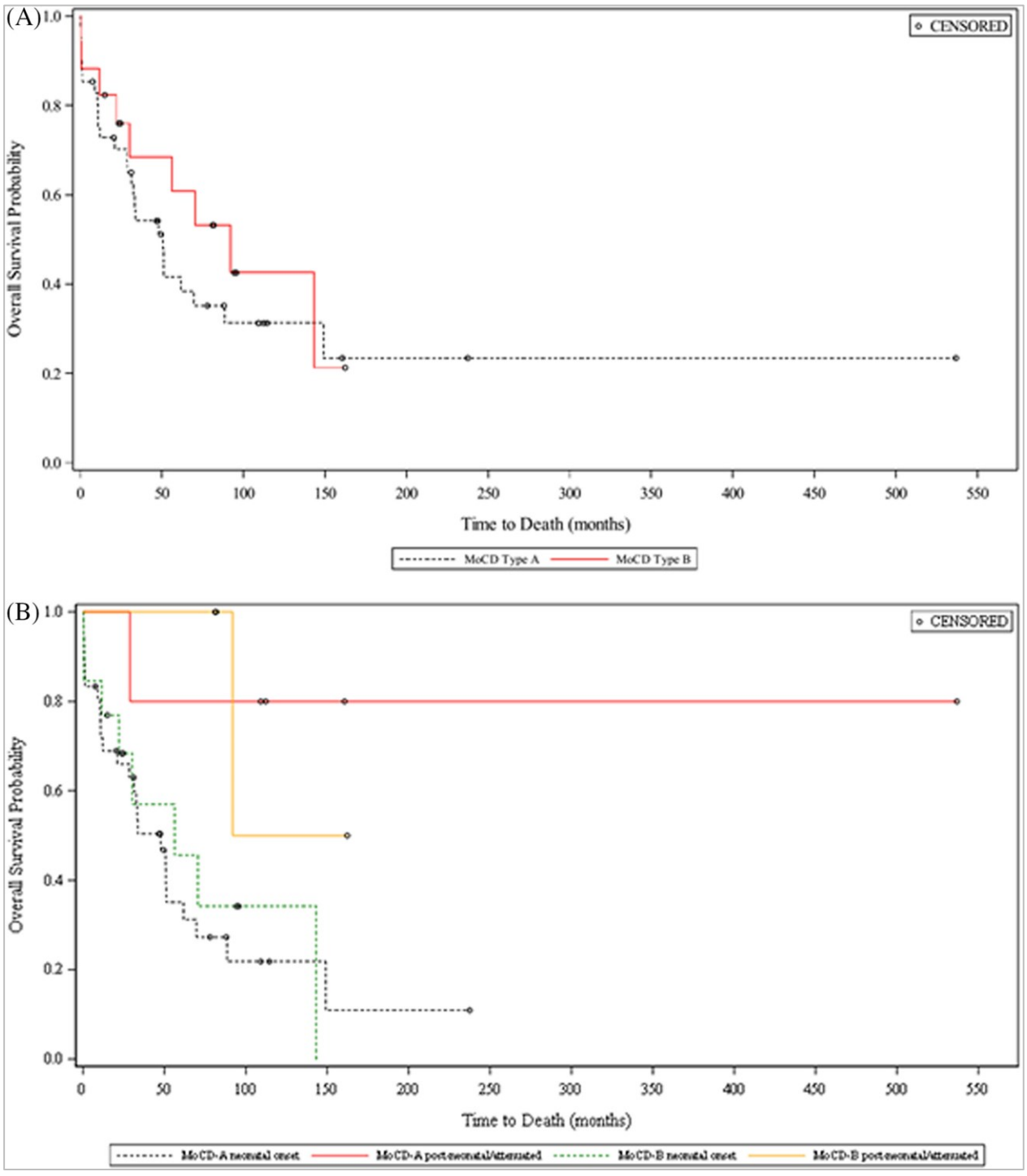
In late-onset MoCD patients, symptom onset is generally within the first 2 years of life; however, diagnosis may occur later. (16) Usually, the clinical manifestations

include developmental delay, lens dislocation, and extrapyramidal, and pyramidal symptoms, all often arising abruptly after an intercurrent illness. Seizures are less common in late-onset MoCD compared to the classical form. Clinical presentation may be variable, including patients who present with predominant extrapyramidal signs or with an acute neurological deterioration. Basal ganglia and dentate nuclei changes are often recognised as an isolated finding in MRIs of patients with late-onset and mild clinical course. On the other hand, MRI changes in patients with late-onset and severe clinical course present similarly to the early-onset form of MoCD (diffuse brain atrophy, gliosis, arrested development of myelination, and cystic necrosis of cerebral white matter). (16)

B.1.4.4 Mortality

Mortality data are limited for MoCD Type A patients in England. International data, however, show that survival rates are poor; in the absence of treatment, most patients die within the first years of life.(7, 9) In an observational, noninterventional, multinational, natural history study (N=58; MoCD Type A n = 41, Type B n = 17), median survival was 4.23 years for patients with MoCD Type A, with a median age at death of 2.4 years. Among patients with neonatal onset MoCD Type A, 71.8% survived to 1 year of age (median age at death 2.4 years). Please see Figure 5 for the Kaplan-Meier estimates of survival probability for both MoCD Type A and Type B. During the prospective data collection period, one patient died with MoCD Type A (5.1 years old), reportedly due to sepsis and intracranial haemorrhage.(9)

Figure 5: Median survival of patients with MoCD Type A who experienced symptom onset within 28 days of birth (N=58) [i]



Source: Spiegel *et al.* 2022. Kaplan-Meier estimates of survival probability. (A) Full analysis by MoCD type (in the full analysis by MoCD type, MoCD Type A n=41 and MoCD Type B n=17). (B) Neonatal onset and post neonatal onset by MoCD Type (neonatal onset was defined as patients with onset of MoCD by 28 days. Post neonatal onset was defined as patients with onset of MoCD symptoms beyond 28 days of postnatal age. MoCD Type A neonatal onset n=36, MoCD Type A post neonatal onset/attenuated n=5, MoCD Type B neonatal onset n=13, and MoCD Type B post neonatal onset/attenuated n = 4). Abbreviations: MoCD=molybdenum cofactor deficiency; No.=Number (9).

In a comprehensive analysis of studies published from 1980 to 2013 (N=82), median survival was calculated to be 36 months for patients with any type of MoCD.(7) Another study showed that patients with genotypes typically associated with severe pathogenicity had a median survival of 15 months (standard deviation (SD): 1.83).(18)

B.1.4.5 Effect of MoCD Type A on quality of life of patients

Because MoCD Type A is ultra-rare, with severe symptoms affecting development, communication and cognition, there is a paucity of data surrounding the quality of life of patients with the condition. However, the clinical manifestations discussed above are representative of the disease's rapid and irreversible neurodegenerative pathophysiology. MoCD Type A is life-altering and presents serious caregiver challenges, as patients have difficulty feeding, sitting, and speaking. Some patients are bedridden and unable to ambulate at all.(3, 12, 13) This means the impact on quality of life of MoCD Type A on patients and caregivers is profound.

B.1.4.6 Effect of MoCD Type A on quality of life of families/caregivers

There is a large burden associated with caring for individuals with MoCD Type A, impacting caregivers both emotionally and financially. This section assesses the impact of MoCD Type A on caregivers, using proxy disease areas. To ensure that this burden is covered appropriately, the disease journey is split into two phases:

- The acute phase covers initial symptoms e.g., seizures. Proxy diseases and symptomatic states used for this phase include Dravet syndrome and hypoxic-ischaemic encephalopathy (HIE).
- The chronic phase covers developmental and motor issues in addition to seizures experienced by patients with MoCD. The proxy diseases used in this phase are Dravet syndrome and cerebral palsy (CP).(27)

<u>Acute phase</u>

Caregivers of neonates with seizures are confronted with numerous challenges. Interviews reveal that the emotional and physical toll of care, the need to make radical changes to family life, and uncertainty about the future are all key concerns.(28)

A particularly distressing burden experienced by caregivers is the emotional and physical toll of care. Caring for a child with MoCD requires attending frequent medical appointments, administering medicine, finding suitable childcare, and being prepared for emergency hospital visits. Caregivers of children with seizures often describe feelings of helplessness, anxiety, and fear, as well as reporting extra physical activity which leads to exhaustion.(28) Surveys of parents of neonates experiencing seizures show that 54% of caregivers experience symptoms of anxiety and 32% symptoms of depression after their child is discharged from hospital. Similarly, a retrospective questionnaire and prospective 12-week daily diary showed that 45% of caregivers for children with DS reported episodes of depression.(29) In the case of MoCD, the emotional toll is most likely compounded by the awareness that the child will die within a few years.

Another reported burden pertains to uncertainty surrounding prognosis and the length of treatment.(28) Misdiagnosis is common in patients with MoCD,(17) leading to a missed opportunity to intervene with treatment before extensive damage to the CNS has occurred. Furthermore, unnecessary distress can occur as a result of ineffective treatments being administered for a misdiagnosed condition. This demonstrates a high unmet need to intervene optimally.

Chronic phase

Caregivers of patients with MoCD who overcome the initial phase of symptoms must deal with the chronic effects of widespread CNS damage and the deteriorating physical and neuro-developmental functioning of the child.

Caregivers of children with MoCD are likely to experience similar difficulties to those of children with CP.(27) Interviews with parents of children with CP in low and middle-income settings (30) showed that caregivers experienced a considerable physical burden due to additional difficulties moving, cleaning, feeding, playing with, and providing physical therapy to the child. They also reported feeling guilty for being unable to provide equal attention to healthy siblings. Financial difficulties were another source of anxiety for caregivers.(30)

Caregivers of children with MoCD are confronted by potentially life-changing choices, similar to those described by caregivers of children with similar

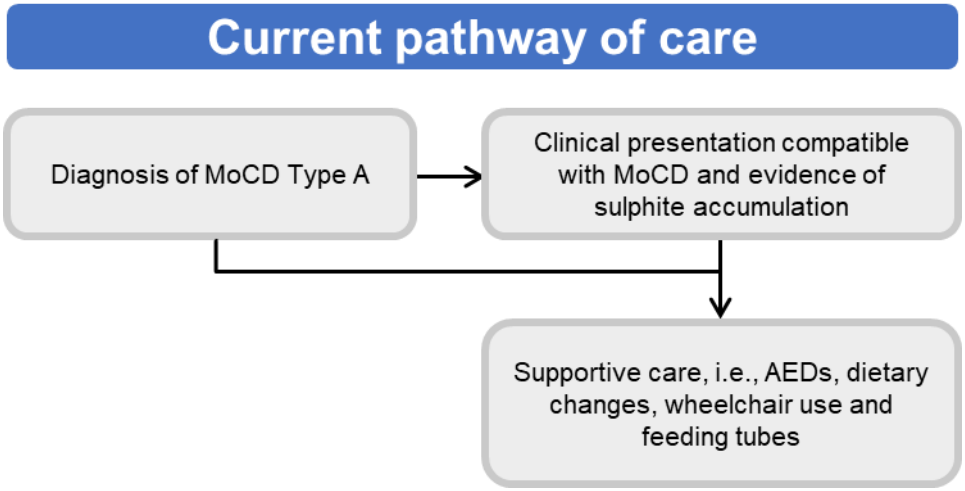
encephalopathies. A study found that 80% of caregivers reported that caring for a child with DS had influenced their ability to work, with 81% of those who were unemployed citing the reason for their unemployment as ‘giving up their job because of their caregiver responsibilities’. Absenteeism was common among employed caregivers (61%), with 65% reporting that they had taken time off work in the past four weeks to care for their child. Time taken off work for childcare is frequently deducted from salaries, holiday allowance, or sick leave (64% reported this happened at least sometimes). Caring for a patient with DS also affects caregivers’ social lives; nearly all caregivers (91%) indicated that caring for a child with DS makes daily activities, family relationships, and social life difficult. Most caregivers (77%) reported having less than one hour per day to themselves for relaxing or social activities.(31)

B.1.5 Current treatments and unmet need

There are no relevant guidelines on MoCD Type A in England or internationally, including those from the National Institute for Health and Care Excellence (NICE), NHS England, or other organisations. Best practice is uncertain and tailored to each individual patient.

In the current clinical pathway for patients with MoCD Type A, depicted in **Error! Reference source not found.**, the lack of specific guidelines and licensed treatments necessitates a focus on BSC. This means that the treatment pathway focuses either on relieving symptoms associated with the disease, or supportive care for the patient.(3, 7, 20-24) The goal of BSC is to address the severe symptoms, issues, comorbidities, and complications associated with MoCD Type A. Typically, though, it falls short of addressing the underlying cause of the disease and does not address the condition's high mortality rate.

Figure 6: Current pathway of care



Abbreviations: AEDs = anti-epileptic drugs; MoCD = molybdenum cofactor deficiency.

Current AEDs are employed to reduce the severity and frequency of seizures, but their effectiveness is limited to alleviating short-term symptoms; they do not address the underlying disease process.(2, 20) The mechanism of actions of AEDs variously target the modulation of voltage-gated ion channels (sodium, calcium, and potassium channels), inhibit γ-aminobutyric acid (GABA), directly modulate synaptic release, or inhibit synaptic excitation.(32) Fundamentally, AEDs do not address the build-up of sulphites in the body, which is the primary cause of the symptoms experienced by patients with MoCD.

Diet changes, particularly low-sulphur diets, have been used in several case studies to reduce the unusually high levels of sulphite and SSC ingested by patients. However, the benefits of diet on clinical outcomes are limited, and it is not thought to have an impact on modifying the course of disease in severe MoCD.(23)

These approaches have shown limited effectiveness in improving the overall prognosis for patients with MoCD. Seizures may persist or remain difficult to control despite medication, and long-term survival rates are still poor. Furthermore, the neurological and developmental impairments associated with MoCD often continue to progress, impacting the quality of life of both affected individuals and their families.

As MoCD Type A progresses, the impact on quality of life is likely to worsen. The current lack of treatments means that the trajectory of the disease remains poor.

There is a high unmet need for a transformative therapy, such as fosdenopterin, to address the underlying cause of the condition.

B.1.6 Introduction to fosdenopterin

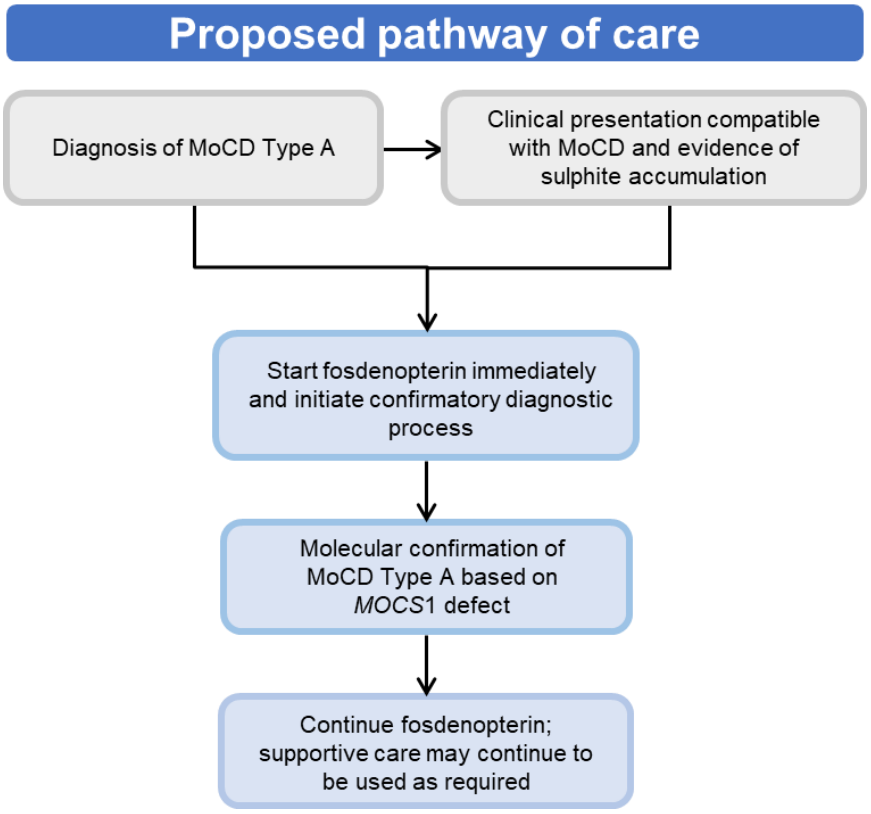
Fosdenopterin is a substrate replacement therapy which provides an exogenous source of cPMP, restoring MoCo synthesis and ultimately reducing the pathologically elevated sulphite and SSC levels associated with MoCD Type A.(33) Fosdenopterin was given orphan designation by the EMA on 20th September 2010 (EU/3/10/777) and was approved by the EMA under exceptional circumstances in September 2022, making it the first medicine approved in Europe to treat patients with MoCD Type A. Fosdenopterin is to be administered if the patient has a presumptive diagnosis of MoCD Type A or a confirmed diagnosis of MoCD Type A. Patients with a presumptive diagnosis of MoCD Type A need to have a genetic test to confirm the diagnosis of MoCD Type A. Fosdenopterin must be discontinued if the MoCD Type A diagnosis is not confirmed by genetic testing. The therapy was approved by the US FDA in February 2021 and by the Israel Ministry of Health in July 2022.

The efficacy and safety of fosdenopterin are supported by data from 15 treated patients and 37 natural history controls.(34-37) Treatment with fosdenopterin demonstrated a significant improvement in overall survival, supported by positive effects on growth, motor function and disease biomarkers. The introduction of fosdenopterin to clinical practice will represent a life-saving and meaningful improvement for MoCD Type A patients, as the therapy significantly improves overall survival and has the potential to improve HRQoL.(34-37)

B.1.7 The positioning of fosdenopterin in the clinical pathway of care

Fosdenopterin would be available as a first-line treatment to all patients with a presumptive and/or genetically confirmed diagnosis of MoCD Type A; currently, there is one eligible patient in England. In Figure 7**Error! Reference source not found.**, a proposed pathway of care for a patient with MoCD Type A is illustrated.

Figure 7: Proposed pathway of care



Abbreviation: MoCD = molybdenum cofactor deficiency; *MOCS*1 = *molybdenum cofactor synthesis* 1.

The pathway begins with a clinical presentation that is compatible with MoCD and evidence of sulphite accumulation. Treatment is started immediately, and a confirmatory diagnostic process is initiated. The confirmatory diagnostic process involves genetic testing to confirm a *MOCS1* defect, which causes MoCD Type A. Treatment should be administered up to, and following, molecular confirmation of the *MOCS1* defect.

Optimal treatment relies on promptly addressing the patient's condition, specifically by initiating treatment upon suspicion of MoCD Type A. Ensuring that patients receive treatment before the onset of severe neurological damage is crucial, as the consequence of delayed intervention can significantly compromise patient outcomes.

B.1.8 Equality considerations

The company does not anticipate any equality issues associated with the introduction of fosdenopterin to clinical practice.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

The relative efficacy assessment is based on a systematic literature review carried out in March 2023, which was conducted according to the principles of systematic reviewing published in the Cochrane Handbook, and the NICE Methodology Process and Methods guide. The SLR search strategy and study selection methods are described in Appendix D.

In total, 18 studies met the inclusion criteria of this SLR. 11 were case reports, 4 were case series reports, one was an observational prospective cohort study, one was a comprehensive review, and one was a retrospective natural history study.

Table 4 provides a list of studies specifically reporting on the efficacy or safety of treatment with cPMP that were included in this SLR.

Table 4: List of included studies

Author	Treatment/s reported	Full citation	Number of patients	Country	Publication type	Study type
Bowhay. 2012	cPMP	Bowhay S. Two years experience of the treatment of molybdenum cofactor deficiency. Archives of Disease in Childhood. 2013;98(6):e1-e.	2	UK	Abstract	Case series
Confer *et al.* 2021	cPMP	Confer N, Basel D, Blankenbiller T, Squires L. Increased survival in MoCD type A patients treated with cPMP when compared to a natural history cohort. Molecular Genetics and Metabolism. 2021;132:S63-S4.	49	NR	Abstract	Retrospective natural history study
Hişmi *et al.* 2015	cPMP, esmolol, propranolol and phenobarbital	Hişmi B SÜ, Veldman A, Özçelik A, Santamaria-Araujo J A5, Coskun T, Sivri S, Tokatli A, Karlı-Oğuz K, Schwarz G. P-175 Cyclic pyranopterin monophosphate treatment trial in a newborn with molybdenum cofactor type A deficiency. J Inherit Metab Dis. 2015;38:S35-378.	1	NR	Poster	Case report
Hitzert *et al.* 2012	cPMP	Hitzert MM, Bos AF, Bergman KA, Veldman A, Schwarz G, Santamaria-Araujo JA, *et al.* Favorable outcome in a newborn with	1	Netherlands	Journal publication	Case report

		molybdenum cofactor type A deficiency treated with cPMP. Pediatrics. 2012;130(4):e1005-e10.				
Schwahn *et al.* 2010	cPMP	Schwahn B, Galloway P, Bowhay S, Veldman A, Santamaria-Araujo J, Schwarz G, *et al.* SUCCESSFUL TREATMENT OF TWO NEONATES WITH MOLYBDENUM COFACTOR DEFICIENCY (MOCD) TYPE A, USING CYCLIC PYRANOPTERINE MONOPHOSPHATE (CPMP). Journal of Inherited Metabolic Disease. 2010;33:S29-S.	2	UK	Abstract	Case series
Schwahn *et al.* 2011	cPMP	Schwahn B, Galloway P, Bowhay S, Veldman A, Belaidi A, Santamaria-Araujo J, *et al.* FOLLOW-UP OF TWO INFANTS WITH MOLYBDENUM COFACTOR DEFICIENCY (MOCD) GROUP A, ON LONG-TERM TREATMENT WITH CYCLIC PYRANOPTERIN MONOPHOSPHATE (CPMP). Journal of Inherited Metabolic Disease. 2011;34:S84-S.	2	UK	Abstract	Case series
Schwahn *et al.* 2015	cPMP	Schwahn BC, Van Spronsen FJ, Belaidi AA, Bowhay S, Christodoulou J, Derks TG, *et al.* Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015;386(10007):1955-63.	11	Australia, Germany, UK, Netherlands, Germany, USA	Journal publication	Observational prospective cohort study
Spronsen *et al.* 2010	cPMP	Spronsen F, Schwarz G, Meiners L, Lunsing I, Bouman K, Erwich J, *et al.* Molybdenum Cofactor Type A Deficiency (MoCD-A) May Result In Fetal Changes In Late Pregnancy, Which Can Be Successfully Reversed With cPMP. Journal of Inherited Metabolic Disease. 2010;33:S30-S.	1	NR	Abstract	Case report
Veldman *et al.* 2010	cPMP	Veldman A, Santamaria-Araujo JA, Sollazzo S, Pitt J, Gianello R, Yaplito-Lee J, *et al.* Successful treatment of molybdenum cofactor deficiency type A with cPMP. Pediatrics. 2010;125(5):e1249-54.	1	Australia	Journal publication	Case report

Veldman *et al.* 2011	cPMP	Veldman A, Schwahn B, Galloway P, Spronsen F, Bergman K, Weis I, *et al.* EFFICACY AND SAFETY OF CYCLIC PYRANOPTERIN MONOPHOSPHATE IN THE TREATMENT OF SIX NEWBORN PATIENTS WITH MOLYBDENUM COFACTOR DEFICIENCY TYPE A. Journal of Inherited Metabolic Disease. 2011;34:S84-S.	6	NR	Abstract	Case series

Abbreviations: NR = not reported. †Schwahn *et al.* 2021 was a review article on substrate replacement therapy as a treatment for MoCD Type A. However, due to the nature of the study, the number of patients and their geographic distribution could not be determined.

Ten studies reported efficacy analyses of cPMP treatment for patients with MoCD Type A, (38-47) and four studies reported the safety of substrate replacement therapy.(41, 44, 46, 48) Overall, four studies were identified as providing relevant clinical effectiveness for inclusion in the model: Studies MCD-501, MCD-201, MCD-202 and MCD-502. Evidence on the efficacy of substrate replacement therapy is presented in the following section.

B.2.2 List of relevant clinical effectiveness evidence

Because it would be unethical to conduct placebo-controlled trials in patients with MoCD Type A (considering the rarity of the disease and lack of treatment options for this population), MCD-502, a retrospective and prospective natural history study, was conducted to provide a control cohort for comparison.

To fully evaluate the efficacy of the cPMP therapy, a comparative analysis was performed based on patient data from studies MCD-501, MCD-201, and MCD 202, as well as from natural history patients in study MCD-502. The studies were conducted with rcPMP in study MCD-501 and fosdenopterin (cPMP) in study MCD-201 and MCD-202; rcPMP and cPMP are considered to have identical active moieties. To reflect the fact that cPMP and rcPMP have the same active moieties, fosdenopterin is referred to as cPMP when discussing the study design and results in this section.

Demographics, baseline characteristics, and efficacy data from the studies were integrated for the analysis. The efficacy endpoints assessed across studies included overall survival, changes to MoCD Type A-associated biomarkers, feeding patterns,

growth parameters, developmental progress, and seizures. The combined data generated results displaying the full benefit of fosdenopterin treatment for the proposed indication. Table 5 presents an overview of the studies included in the integrated efficacy analysis.

Table 5: Overview of relevant clinical effectiveness studies

Study	MCD-501	MCD-201	MCD-202	MCD-502
Study design	A retrospective, observational, noninterventional data collection study	A Phase 2, multicentre, multinational, open-label, dose escalation study	A Phase 2/3, multicentre, multinational, open-label study	Natural history study, retrospective and prospective, multinational, multicentre
Population	Paediatric patients with MoCD Type A, N=4	Paediatric patients with MoCD Type A, previously treated with rcPMP, N=8	Paediatric patients up to 5 years of age with confirmed or suspected MoCD Type A, N=3	Paediatric patients with MoCD Type A, N=37
Intervention(s)	rcPMP	cPMP	cPMP	Natural history
Comparator(s)	Not applicable	Not applicable	Not applicable	Not applicable
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	Yes	Yes
Rationale if study not used in model	Not applicable	Not applicable	Not applicable	Not applicable
Reported outcomes specified in the decision problem	The following outcomes individually address one or more of the outcomes specified in the decision problem: • Survival • Growth parameters • Disease characteristics and progression	The following outcomes individually address one or more of the outcomes specified in the decision problem: • Change from baseline in urine and blood SSC levels • Change from baseline in clinical findings from neurological examination	The following outcomes individually address one or more of the outcomes specified in the decision problem: • Overall survival • Changes from baseline in MoCD Type A-related biomarkers • Changes from baseline in growth parameters	The following outcomes individually address one or more of the outcomes specified in the decision problem: • Survival at 1 year of age for patients with MoCD Type A • Growth parameters • Weight • Height • Seizure activity

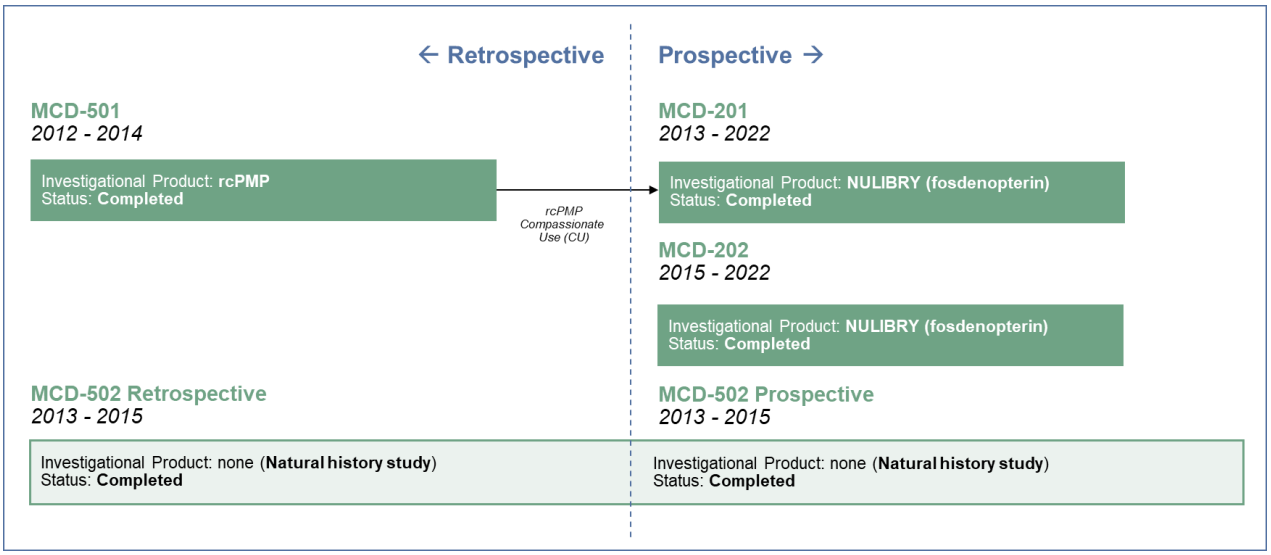
Study	MCD-501	MCD-201	MCD-202	MCD-502
	• Feeding patterns • Neurologic examination • Developmental assessments • Safety • Biomarkers • Neurophysical development • Ophthalmologic and hearing assessments • Neuroimaging for anatomical development	• Change from baseline in age-appropriate motor and cognitive assessments • Change from baseline in seizure frequency • Changes in growth parameters • Change from baseline in feeding patterns • Change from baseline in neuroimaging • Change from baseline in MoCD-associated urine and blood biomarker levels including, but not limited to, uric acid and xanthine	• Change from baseline in feeding patterns • Change from baseline in age-appropriate motor and cognitive assessments • Neurologic examination • Time course of clinical evidence of seizure activity • Change from baseline in brain ultrasound imaging (neonates only) • Change in brain MRI findings • Ophthalmologic examination	• Neurologic assessments • Neurocognitive and development assessments • Feeding patterns • Clinically significant medical events • Biochemical markers • Head circumference • Neuroimaging findings • Physical examination • Vision and hearing assessments
All other reported outcomes	Not applicable	Pharmacokinetic parameters	Pharmacokinetic parameters	Not applicable

Abbreviations: cPMP=cyclic pyranopterin monophosphate; MoCD=molybdenum cofactor deficiency; MRI=magnetic resonance imaging; rcPMP=recombinant cyclic pyranopterin monophosphate.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

An overview of the clinical study designs of MCD-501, MCD-201, MCD-202, and MCD-502 is presented in Figure 8.

Figure 8: Overview of clinical studies



Abbreviations: rcPMP=recombinant cyclic pyranopterin monophosphate.

Given the ultra-rare nature of MoCD Type A, decentralised strategies for site selection and clinical trial recruitment were employed throughout the development programme. The centres approached were based on a review of published case reports, the existence of a known patient protocol, or verbal communication of a potential case. Given the genetic basis of the disease, there was a high degree of regional overlap in the sites across studies MCD-502, MCD-501, MCD-201, and MCD-202, including in Germany, Israel, the Netherlands, Tunisia, Turkey, and the UK. The centres selected and activated in MCD-501, and consequently included in MCD-201, were at the same centres or in centres nearby to where patients with MoCD Type A were receiving rcPMP via named-patient treatment plans. MCD-502 was conducted in 14 countries by 27 investigators who had previously diagnosed or treated patients with MoCD. Additional measures for recruitment in MCD-502 were taken in the US given the rarity of the disease, including contacting state newborn screening centres for potential patients.

B.2.3.1 Trial design

MCD-501 was a retrospective, observational, noninterventional data collection study for patients with MoCD Type A who had previously been treated with recombinant cPMP in a named-patient programme.

MCD-201 was a Phase 2, multicentre, multinational, open-label study designed to evaluate the safety and efficacy of fosdenopterin administered to infants and children with MoCD Type A pre-treated with rcPMP. The study also includes an intra-patient dose escalation to determine the safe starting dose for future studies. The initial treatment period was 6 months, which was followed by an extension period where patients continued to be treated and observed.

MCD-202 was a prospective, multicentre, multinational, open-label study designed to evaluate the efficacy and safety of fosdenopterin in patients with MoCD Type A. The main study period consisted of a 12-month treatment period, after which patients were followed up for 36 months in a long-term extension period. After 36 months, patients continued to be followed every 6 months.

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

B.2.3.2 Study eligibility criteria

Table 6 presents the main inclusion criteria for patients included in studies in the integrated analysis.(34-37)

Table 6: Main inclusion criteria of studies MCD-501, 201, 502 and 202

Study number	Main inclusion criteria
MCD-501	Included male and female patients of any age with MoCD Type A, suspected Type A, or Type B who previously received rcPMP only by IV route of administration and for whom parents or legal guardians voluntarily provided written informed consent
MCD-201	• Male or female patients with a genetically confirmed diagnosis of MoCD Type A (*MOCS1* mutations) • Currently treated with rcPMP infusions through named-patient use with rcPMP
MCD-202	Male or female neonatal (1 to 28 days of age, inclusive, at the time of fosdenopterin administration, with Day 1 of age corresponding to the Day of birth), infant (29 days to < 2 years of age) or child patients (2 to 5 years of age

	[inclusive]) with MoCD Type A, previously untreated with fosdenopterin or treated with fosdenopterin through the compassionate use In neonates, diagnosis of MoCD Type A, based on: • Prenatal genetic diagnosis, or • Onset of clinical and/or laboratory signs and symptoms consistent with MoCD Type A (e.g., seizures, exaggerated startle response, high-pitched crying, truncal hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulphite and/or SSC, elevated xanthine in urine or blood, or low or absent uric acid in the urine or blood) within the first 28 days after birth In infants or children, diagnosis of MoCD Type A, based on: • Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may have been obtained after initiation of fosdenopterin therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A
Study MCD-502	Both living and deceased patients of any age were considered for study inclusion. Main inclusion criteria: • Documented clinical and biochemical diagnosis or genetic diagnosis of MoCD or isolated SOX deficiency. Biochemical criteria were either 1) high urine, serum, or plasma levels of SSC or 2) a positive urine sulphite dipstick in at least two samples

Source: MCD-501, MCD-201, MCD-202, and MCD-502 clinical study reports (CSRs).(34-37)

B.2.3.3 Trial drugs

Table 7 provides a summary of treatments that patients received in each study.(34-37)

Table 7: Treatments received in each study

Study number	Treatments received in study
MCD-501	This study was a retrospective, observational, noninterventional data collection study. Patients had previously received rcPMP treatment following the named-patient treatment plans.
MCD-201	During the 6-month initial treatment period, patients began daily IV infusions of fosdenopterin on study Day 1; the Day 1 dose was matched to their current rcPMP dose. Patients received their first dose of fosdenopterin approximately 24 hours after their last treatment with rcPMP. No further treatments with rcPMP were allowed during the study.
MCD-202	Dosing began as soon as possible after birth for neonate patients and was based on a patient's GA. Day one dosing for term (≥37 weeks GA) and preterm (<37 weeks GA) neonates began with fosdenopterin IV infusions of 700 and 525 µg/kg/day, respectively. For all patients, the first dose adjustment was scheduled to occur at Day 28 with incremental increases up to 1300 µg/kg/day by Month 9. However, dosing may have been escalated on or before Day 28, based on the Investigator and SRC/DMC review of all available data.
MCD-502	This study was limited to data collection; no investigational medicinal product or any other exploratory therapy was administered.

Source: MCD-501, MCD-201, MCD-202 and MCD-502 CSRs.(34-37)

B.2.3.4 Objectives

Table 8 presents primary and secondary objectives of each of the studies included in the integrated analysis.(34-37)

Table 8: Primary and secondary objectives of studies included in the integrated analysis

Study number	Objectives of the study
MCD-501	The primary objective of this retrospective observational study was to assess the safety and efficacy of prior administration of intravenous (IV) rcPMP in patients with a genetically confirmed diagnosis of MoCD Type A or who were suspected to have a diagnosis of MoCD Type A based on signs and symptoms at the time of rcPMP treatment initiation.
MCD-201	The primary objective of this clinical study was to evaluate the safety of fosdenopterin over the first 6 months of treatment. The secondary objectives of this clinical study were: • To characterise the pharmacokinetics (PK) of increasing doses of fosdenopterin • To evaluate the effect of fosdenopterin on urine and blood SSC levels • To evaluate the effect of fosdenopterin on neurologic, motor, and cognitive functions • To evaluate the effect of fosdenopterin on CNS structure

	• To evaluate the long-term safety of fosdenopterin The exploratory objective of this clinical study was to describe the effect of fosdenopterin on MoCD-associated urine and blood biomarker levels, including, but not limited to, uric acid and xanthine.
MCD-202	The primary objective of this clinical study was to evaluate the safety and efficacy of fosdenopterin in neonate, infant, and paediatric patients with MoCD Type A who were either treatment-naïve or who had received compassionate use fosdenopterin. The secondary objectives of this clinical study were: • To evaluate the effect of fosdenopterin on MoCD Type A-associated urine and blood biomarker concentrations • To evaluate the effect of fosdenopterin on growth and development using age-appropriate assessments • To evaluate the effect of fosdenopterin on paediatric measures of functional ability and activities of daily living • To characterise the PK of fosdenopterin and the impact on pharmacodynamic (PD) biomarkers • The exploratory objectives of this study were the following: • To identify clinical measures that may be useful for characterising MoCD Type A • To further characterise changes in MoCD Type A-associated urine and blood biomarker concentrations
MCD-502	The primary objective of the study was to characterise the natural history of MoCD Type A, the most common subtype of MoCD, in terms of survival. The secondary objectives of the study were: • To evaluate levels of the biochemical markers SSC, uric acid, and xanthine in blood and urine over time in patients with MoCD and isolated SOX deficiency • To quantitate the natural history of MoCD Type A, Type B, Type C, unspecified type, and isolated SOX deficiency in terms of changes in head circumference, seizure frequency, and neurocognitive outcomes • To evaluate changes in CNS morphology, as measured by brain MRI, in patients with MoCD and isolated SOX deficiency • To correlate biochemical marker levels with changes in head circumference, seizure frequency, neurocognitive outcomes, and MRI findings • To quantitate the natural history of MoCD Type B, MoCD Type C, MoCD of an unspecified type, and isolated SOX deficiency in terms of survival

Source: MCD-501, MCD-201, MCD-202 and MCD-502 CSRs.(34-37)

B.2.3.5 Recruitment

Study MCD-501

Informed consent was acquired between 1st November 2012 and 7th October 2014. Fifteen patients enrolled in the study: 10 patients with MoCD Type A, 4 patients with MoCD Type B, and one patient with MoCD of an unknown type. This study was

conducted at 13 centres that had previously treated paediatric patients with rcPMP, located in Australia, Germany, Netherlands, Turkey, the United Kingdom, and the United States.

Study MCD-201

The first patient was enrolled on 2nd April 2014, and the study was completed in 2022. In total, eight patients were enrolled. with seven patients having completed through Month 54, and the eighth patient having completed through Month 6. Three patients have completed through Month 72, and one patient has completed study visits through Month 78. The study was conducted at five study centres in five countries (Australia, Tunisia, Netherlands, UK, and US). (49)

Study MCD-202

The first patient enrolled on 20th June 2016 and the study was completed in October 2022. Five patients were screened for the study. Four patients were enrolled and received treatment with cPMP. One patient was diagnosed with MoCD Type B and discontinued. The study was conducted at four study centres in three countries (Israel, Norway and two in the United Kingdom). One additional patient was screened at a different site but did not meet the screening criteria and did not receive the study drug.(49)

Study MCD-502

Informed consent was acquired between 24th September 2013 and 11th December 2015. Seventy patients were screened for this study, of whom 65 were enrolled at 27 sites in 14 countries (Canada, Germany, Spain, UK, Israel, Italy, Japan, Malaysia, Netherlands, Poland, Saudia Arabia, Tunisia, Turkey, and US). Of the 65 enrolled patients, 37 patients were diagnosed with MoCD Type A. Of the patients with confirmed MoCD Type A, 17 (46%) patients were enrolled in the living cohort, of whom 14 (38%) patients enrolled in the 12-month prospective data collection period. Thirteen (35%) patients with MoCD Type A completed the prospective data collection period; one patient died before the end of the data collection period.(49)

B.2.3.6 Outcomes/endpoints

An overview of the measures of efficacy in the clinical studies is presented in Table 10. A description of the endpoints followed in the studies is included below.(34-37)

Table 9: Overview of outcomes studied in the evidence base for fosdenopterin

Outcome	Description
Survival status	MoCD Type A is a life-threatening and mostly fatal disease with death commonly occurring in the first few years of life.(7) Survival status was determined for all treated patients in MCD-501, MCD-201, and MCD-202 and for untreated controls in the natural history study, MCD-502.
MoCD-associated biomarkers	Patients with MoCD Type A experience neuronal injury that is severe, rapidly progressive, and often irreversible due to toxic concentrations of sulphite in the brain and formation of SSC.(50) Biomarkers associated with the MoCD pathways analysed across studies include SSC, uric acid, and xanthine in urine and plasma.
Growth	A characteristic of MoCD Type A is failure to thrive, with growth as an important indicator of a child's overall health and nutritional status. When available, growth parameters, including weight, height/length, and head circumference were collected (Table 10).
Feeding patterns	Difficulty with oral feeding is one of the first commonly reported presenting symptoms in infants with MoCD Type A. This difficulty in oral feeding often progresses to require supportive feeding via nasogastric or gastrostomy tubes. Information on feeding patterns, types, and assessments captured across studies are provided in Table 10.
Developmental and functional assessments	Patients with MoCD Type A often develop severe static encephalopathy and developmental delays due to irreversible CNS injuries which have been shown to occur *in utero* or after birth, including subcortical cystic cavitation, hydrocephalus, diffuse cortical atrophy, and basal ganglia injury.(7) Once widespread death of neural cells in the brain occurs, the structural CNS damage is unable to be reversed by cPMP. However, the development of these structural brain manifestations can often be prevented or slowed if the diagnosis is made quickly and cPMP treatment is started as soon as possible after birth.(51) Developmental and functional assessments analysed in the clinical studies included: • The Gross Motor Function Classification System (GMFCS)-ER, Bayley Scales of Infant Development, Third Edition (Bayley-III). The Bayley-III assessed changes in gross motor, fine motor, language, and cognitive development. The Bayley- III was administered to children 3 years of age and under and to patients with severe developmental delay for whom the Wechsler Preschool and Primary Scale of Intelligence-IV – Fourth Edition (WPPSI)-IV was not an appropriate assessment. • Gross Motor Function Classification System-Expanded and Revised (GMFCS-E&R), a 5-level classification system which describes the gross motor function of children and youth (up to 18 years of age) based on their self-initiated movement, with particular emphasis on sitting, walking, and wheeled mobility for children with impaired motor skills. Children with motor functions such as those classified in GMFCS-E&R Level I can generally walk without restrictions but tend to be limited in some of the more

	advanced motor skills. Children with motor function classified as Level V have very little voluntary control of movement, no means of independent mobility even with assistive technology, are generally transported by their caregivers directly or in a wheelchair, and require assistance for all activities of daily living. • WPPSI- IV, an intelligence measure designed for children ages 2 years and 6 months to 7 years and 7 months that comprises 15 subtests from which composite and age-equivalent scores are derived. For patients with severe developmental delay, the WPPSI-IV may not have been an appropriate assessment, and therefore, the Bayley-III may have been administered instead. • Paediatric Evaluation of Disability Inventory (PEDI), which was conducted in Study MCD-202, is a comprehensive clinical assessment of key functional capabilities and performance in children ages 6 months to 7 years. It is administered by interviewing the parent or care provider, who reports on their child's typical performance on each item. Functional ability and activities of daily living are assessed in three domains including self-care (getting dressed, keeping clean, home tasks, and eating and mealtime), mobility (basic movement and transfers, standing and walking, steps, and inclines, running and playing, and wheelchair), and social (interaction, communication, everyday cognition, and self-management functional skills scales).
Neuroimaging	Neuronal damage is severe and often rapidly progressive in patients with MoCD Type A and often apparent in the neonatal period (and in some patients, observed *in utero*) because of the accumulation of toxic concentrations of sulphite in the brain. Brain imaging studies reveal a diffuse pattern of brain atrophy with arrested development of myelination, evidence of gliosis, and cystic necrosis of cerebral white matter. Microcephaly is common.(7) The neuroimaging types and assessments captured across studies are provided in Table 10.
Seizure activity	Seizures are a presenting symptom of MoCD Type A as a result of acute CNS sulphite toxicity and are often refractory to AED therapy.(50) Chronic epilepsy may also develop as a sequelae to structural CNS damage and may be refractory to chronic AED therapy. Information on the seizure assessments collected across studies is provided in Table 10.
Neurological examination	Psychomotor retardation due to progressive structural CNS damage is a commonly reported clinical symptom in patients with MoCD Type A.(44) The neurologic examination of this patient population identifies specific clinical symptoms of MoCD Type A, including lack of spontaneous movements, decreased truncal tone, increased appendicular tone, increased deep tendon reflexes, primitive reflexes, and dystonia. (7) The neurological parameters examined, and assessments conducted across studies, are presented in Table 10.

Source: MCD-501, MCD-201, MCD-202 and MCD-502 CSRs.(34-37)

Table 10: Assessment of efficacy measures across studies

Study:	MCD-502[a] Natural History		MCD-501[a]	MCD-201	MCD-202
Treatment:	None		rcPMP	Fosdenopterin	Fosdenopterin
Data collection:	Retrospective	Prospective	Retrospective	Prospective	Prospective
Biomarkers					
Urine biomarkers:	SSC, UA, xanthine, creatinine	SSC, UA, xanthine, creatinine	SSC, UA, xanthine, creatinine	SSC, UA, xanthine, creatinine, urothione	SSC, UA, xanthine, creatinine, urothione
Blood biomarkers:	SSC, UA, xanthine	SSC, UA, xanthine	None	SSC, UA, xanthine	SSC, UA, xanthine
Laboratory type:	Local	Central	Local	Central	Central
Assessments conducted:	Records collected as available	At enrolment, weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months	Records collected as available	Screen/BL, Days: 1, 4b, 7, 142, 28, 57, 67, 87, 97, 117, 127, 147, 157, 180. Months: 9, 12, 18, 24, 30, 36, 48, 60, 78, every 12 months thereafter, and Safety FUP 1st day of dose adjustment and 7-day FUP following dose adjustment	Screen/BL, Days: 1, 2[b],3[b], 4, 5[b], 6[b], 7, 14, 28, 56. Months: 3, 4b, 5[b], 6, 9,12, 18, 24, 30, 36, and Safety FUP/ETc 1st day of dose adjustment and 7-day FUP following dose adjustment
Growth:	Weight, length/height, head circumference	Weight, length/height, head circumference	Weight, length/height, head circumference	Weight, length/height, head circumference	Weight, length/height, head circumference
Assessments conducted:	All data from birth to 1 month of age, then at intervals not shorter than 1 month through enrolment	At enrolment and then weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months	All available data with suggested time points of BL. Days: 7, 8-14, Months: 1, 3, and then every 3 months	Screen/BL, Days: 7, 14, 28, 60, 90, 120, 150, 180 Months: 9, 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter	Screen/BL, D1, daily through D14. Days: 21, 28, 56. Months: 3, 4, 5, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ETc

Study:	MCD-502[a] Natural History		MCD-501[a]	MCD-201	MCD-202
Feeding status:					
Patterns captured:	Predominant and all	Predominant and all	Predominant and All	Current	Current
Type captured:	Oral, nasogastric, gastrostomy tube, other	Oral, nasogastric, gastrostomy tube, other	Nasogastric, percutaneous endoscopic, oral suck, oral feeding, other	Oral, nasogastric, gastrostomy tube, other	Oral, nasogastric, gastrostomy tube, other
Assessments conducted:	All data from birth to 1 month of age, then at intervals not shorter than 3 months through enrolment	Weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months	All available data with suggested time points of BL, D7, M3; and then every 3 months	Screen/BL, Months: 6, 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter; and Safety FUP	Screen/BL, Days: 1, 5, 7, 14, 28, 56. Months: 3, 4, 5, 6, 12, 18, 24, 30, 36; and Safety FUP/ETc
Developmental assessments					
GMFCS-ER	Records collected as available	Baseline and at Months 6 and 12 as available	Records collected as available	Screen, Days: 28, 90, 180, Months: 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter; and Safety FUP	Months: 12, 24, 36; and Safety FUP/ETc
Bayley-III	Records collected as available	At 3 months of age, and every 6 months as available	Records collected as available	BL, Days: 28, Months: 3, 6, 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter	Days: 28. Months: 3, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ETc
WPPSI	Records collected as available	At 3 years of age and the end of the 1-year prospective evaluation as available	Records collected as available	Screen, Months: 6, 12, 24, 36, 48, 60, 66, 78, every 12 months thereafter; and when appropriate	Days: 28. Months: 3, 6, 9, 12, 18, 24, 30, 36; and Safety FUP/ETc if applicable
Denver	Records collected as available	Baseline and every 3 months thereafter as available	Records collected as available	Not assessed	Not assessed

Study:	MCD-502[a] Natural History		MCD-501[a]	MCD-201	MCD-202
GMFM-88	Not assessed	Not assessed	Not assessed	Not assessed	Day: 28. Months: 3, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ETc
Ability to sit unassisted	As measured by The Denver Developmental Screening Test: Sit - No Support. The Denver does not specify for 30 seconds as measured by Bayley Item #26: Sits without support for 30 seconds Neurologic exam includes the following question: Is the patient able to sit without support for 30 seconds or longer and at what age did the patient achieve this milestone?	As measured by Bayley Item #26: Sits without support for 30 seconds As Measured by The Denver Developmental Screening Test: Sit- No Support The Denver does not specify for 30 seconds	As measured by The Denver Developmental Screening Test: Sit - No Support The Denver does not specify for 30 seconds As Measured by Bayley: item #26: Sits without support for 30 seconds	As measured by Bayley Item #26: Sits without support for 30 seconds	As measured by Bayley Item #26: Sits without support for 30 seconds As measured by the Gross Motor Function Measure-88: Item 24: Sitting on Mat: Maintains, arms free, 3 seconds
PEDI	Not assessed	Not assessed	Not assessed	Not assessed	Months: 6, 12, 24, 36; and Safety FUP/ETc
Neuroimaging					
Types of neuroimaging:	MRI, CT scan, ultrasound	MRI, CT scan, ultrasound	MRI, CT scan, ultrasound	MRI, CT scan	MRI, ultrasound
Results collected:	Normal, abnormal	Normal, abnormal	Normal, abnormal, indeterminate	Normal, abnormal, not clinically significant abnormal, clinically significant	Normal, abnormal, not clinically significant abnormal, clinically significant
Assessments conducted:	Records collected as available.	BL, Months 6 and 12 (if clinical condition allowed).	Records collected as available.	Screen/BL; Months 6, 12, 24, 36, 60, 66, 78; and every 12 months thereafter. Neuroimaging is optional if the patient's	MRI; Screen/BL; Months 24, 36. Additional scans may be requested if clinically indicated and

Study:	MCD-502[a] Natural History		MCD-501[a]	MCD-201	MCD-202
				clinical status has not changed since the Month 6 assessment.	clinical conditions allow.
Seizure activity					
Seizure type captured?	Yes	Yes	Yes	No	No
Seizure counts collected?	No	Yes	Yes	Yes	Yes
Collection method:	Chart review	Daily diary	Chart review	Daily diary	Daily diary
AEDs?	General question on seizure CRF plus Con med page	General question on seizure CRF plus Con med page	Captured on specific CRF	General question on seizure CRF plus Con med page	General question on seizure CRF plus Con med page
Assessments conducted:	Retrospective collection from birth to time of enrolment	Assessed continuously during 12-month observation period	Retrospective data collection included all available data with suggested time points as follows: BL; Days 1-14; Months 1, 2, 3; and every 3 months	During screening period, daily through Days 7, 14, 28, then monthly	During screening period, daily through Days 7, 14, 21, 28, then monthly and the 1st day of dose adjustment and 7-day FUP following dose adjustment
Neurological examinations:					
Parameters examined:	Spontaneous movement, truncal tone, appendicular tone, deep tendon reflexes, primitive reflexes, dystonic, opisthotonic, clonus, ambulation, communication	Spontaneous movement, truncal tone, appendicular tone, deep tendon reflexes, primitive reflexes, dystonic, opisthotonic, clonus, ambulation, communication	Spontaneous movement, truncal tone, appendicular tone, deep tendon reflexes, primitive reflexes	Spontaneous movement, truncal tone, appendicular tone, deep tendon reflexes, primitive reflexes, dystonic, opisthotonic, clonus, ambulation, communication	Spontaneous movement, truncal tone, appendicular tone, deep tendon reflexes, primitive reflexes, dystonic, opisthotonic, clonus

Study:	MCD-502[a] Natural History		MCD-501[a]	MCD-201	MCD-202
Assessments conducted:	Retrospective data collection included all data from birth to 1 month of age. Data from 1 month to time of enrolment collected at intervals not shorter than 1 month	At enrolment and then weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months	Retrospective data collection included all available data with suggested time points as follows: BL; Days 7, 14; Months 1, 2, 3; and then every 3 months	Screen/BL; Days 1, 4, 7, 14, 28, 60, 90, 120, 150, 180; Months 9, 12, 18, 24, 30, 36, 42 48, 54, 60, 66, 72, 78 and every 12 months thereafter; the first day of any dose adjustment; the 7-day FUP following any unscheduled dose adjustment; any Safety FUP	Screen/BL; Days 1, 4, 7, 14, 28; Months 3, 4, 5, 6, 9, 12, 18, 24, 30, 36; Safety FUP/ETc; the 1st day of any dose adjustment; 7-day FUP following dose adjustment

Source: European Public Assessment Report (EPAR), EMA. June 2022. Abbreviations: AEDs=anti-epileptic drugs; BL=baseline; Bayley=The Bayley Scales of Infant Development, Third Edition; CRF=case report form; CT=computerised tomography; ET=end of treatment; FUP=follow-up; GMFCS-ER=Gross Motor Function Classification System, Expanded and Revised; MRI=magnetic resonance imaging; PEDI=Paediatric Evaluation of Disability Inventory; rcPMP=recombinant sourced cyclic pyranopterin monophosphate; Screen=screening; SSC=s-sulphocysteine; UA=uric acid. MCD-502 also collected available data on homocysteine, methionine, taurine, hypoxanthine, sulphite, and thiosulfate in urine, and homocysteine, methionine, taurine, and hypoxanthine in plasma. MCD-501 also collected available data on sulphite and thiosulfate in urine. [b] Assessments on these days were conducted in urine only.

B.2.3.7 Demographics and baseline characteristics

Demographics and baseline characteristics are presented for the integrated analysis population. Patient demographics were generally balanced between the cPMP-treated and untreated populations (Table 11).

Table 11: Patient demographics (Full analysis set [FAS] and genotype-matched analysis set (GMAS), patients with MoCD Type A, marketing authorisation application data cut-off 30th October 2020 and MAA safety update data cut-off 31st October 2021)

Parameter statistic	cPMP-treated patients (FAS and GMAS)				Untreated controls	
	MCD-501 only (N=4) †	MCD-201 (N=8)	MCD-202 (N=3)	Total (N=15)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Gender, n (%)						
Male	3 (75.0)	3 (37.5)	1 (33.3)	7 (50.0)	28 (75.7)	13 (68.4)
Female	1 (25.0)	5 (62.5)	2 (66.7)	8 (53.3)	9 (24.3)	6 (31.6)
Race, n (%)						
White	4 (100)	5 (62.5)	2 (66.7)	11 (73.3)	21 (56.8)	12 (63.2)
Asian	0	3 (37.5)	1 (50.0)	4 (28.6)	10 (27.0)	4 (21.1)
Black or African-American	0	0	0	0	0	0
Other	0	0	0	0	6 (16.2)	3 (15.8)
Ethnicity, n (%)						
Hispanic or Latino	1 (25.0)	0	0	1 (6.7)	2 (5.4)	0
Not Hispanic or Latino	3 (75.0)	8 (100)	2 (66.7)	13 (86.7)	31 (83.8)	15 (78.9)
Not Reported/ Unknown	0	0	1 (33.3)	1 (6.7)	4 (10.8)	4 (17.6)
Gestational age						
n	4	8	3	15	30	16
Mean (SD)	37.4 (1.78)	38.8 (1.52)	38.1 (1.85)	38.3 (1.65)	39.0 (1.19)	39.0 (0.90)
Median	37.7	39.0	38.0	39.0	39.0	39.0
Min, max	35, 39	36, 41	36.3, 40	35, 41	36, 41	37, 40.3

Source: EMA D166 update (2022). Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=Full Analysis Set; GMAS=Genotype- Matched Analysis Set; NA=not applicable; rcPMP=recombinant Escherichia coli-derived cPMP; SD=standard deviation. †Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Table 12 summarises the patient baseline disease characteristics for the FAS and GMAS as of the data cut-off date of 31st October 2021. These results show the

comparability of the treated patient population and the untreated control group for MoCD Type A disease manifestations.

Median age at onset of first MoCD signs or symptoms was similar in the treated patients (1 day of age) and the untreated controls (2 days of age); however, the maximum time to onset was shorter for treated patients (maximum of 5 days of age) compared with untreated controls (maximum of 2.6 years of age). The median age at genetic diagnosis in the treated patient group was 4 days and ranged from -181 to 757 days, including four patients who were diagnosed *in utero*. In the untreated control patients, the median age at diagnosis was longer at 269 days (8.8 months) and ranged from 4 days to 40.3 years.

In the FAS, many patients had onset of first MoCD signs and symptoms within 28 days of birth (treated, 93.3%; untreated, 89.2%). The most common presenting signs and symptoms of MoCD in both the treated patients and untreated control patients, with a similar incidence across these groups were: seizures (treated,66.7%; untreated, 91.9%), feeding difficulties (treated, 60.0%; untreated, 60.9%), high-pitched crying (treated, 46.7%; untreated, 43.2%), and exaggerated startle response (treated, 35.7%; untreated, 32.4%). Seizures were reported *in utero* or during the neonatal period in many patients (treated, 78.6%; untreated, 70.3%). A higher proportion of patients in the untreated control group had late-onset seizures (21.6%) compared with the treated patient group (7.1%).

At the data cut-off of 31st October 2021, baseline disease characteristics for the untreated population were similar in the GMAS and FAS. Similarly, the baseline disease characteristics for the prospective full analysis set (PFAS) were consistent with those observed in the FAS.

Table 12: Baseline disease characteristics (FAS and genotype-matched analysis set, MAA data cut-off 30th October 2020 and MAA safety update data cut-off 31st October 2021)

Parameter statistic	cPMP-treated patients (FAS and GMAS)				Untreated controls	
	MCD-501 only (N=4) †	MCD-201 (N=8)	MCD-202 only (N=3)	Total (N=15)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Age at genetic diagnosis (days)						
n	4	8	3	15	30	16

Parameter statistic	cPMP-treated patients (FAS and GMAS)				Untreated controls	
	MCD-501 only (N=4) †	MCD-201 (N=8)	MCD-202 only (N=3)	Total (N=15)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Mean (SD)	-28.0 (86.29)	-29.3 (84.74)	171.7 (507.17)	11.3 (220.96)	1299.6 (2875.20)	435.0 (521.86)
Median	10.0	3.0	-105	4.0	269.0	173.5
Min, max	-157, 25	-181, 59	-137, 757	-181, 757	4, 14708	4, 1683
Age at onset of first MoCD symptoms (days)						
n	4	8	2[d]	14	37	19
Mean (SD)	1.8 (0.96)	1.5 (1.41)	1.0 (0.00)	1.5 (1.16)	55.1 (192.70)	16.6 (50.83)
Median	1.5	1.0	1.0b	1.0	2.0	2.0
Min, max	1, 3	1, 5 [a]	1, 1[b]	1, 5 [a]	1, 927	1, 222
Age at first MoCD symptom category						
≤ 28 days	4 (100)	8 (100)	2 (100)	14 (100)	33 (89.2)	17 (89.5)
28 days	0	0	0	0	4 (10.8)	2 (10.5)

Source: EMA D166 update (2022). Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=Full Analysis Set; GMAS=Genotype-Matched Analysis Set; Max=maximum; Min=minimum; MoCD=molybdenum cofactor deficiency; A=not applicable; rcPMP=recombinant Escherichia coli-derived cPMP; SD=standard deviation. Note: Hypertonia, hypotonia, and encephalopathy were not collected as signs/symptoms in the MCD-501 and MCD-502 studies. [a] The maximum of 5 days is based on a patient with a missing day for the onset of first signs and symptoms; the missing day was imputed using the 15th of the month and based on this patient's date of birth, the first symptoms could have occurred from 1 day to 21 days of age. [b] Patient was diagnosed *in utero* and initiated treatment with cPMP before the onset of signs and symptoms; patient is included as having onset within ≤ 28 days of birth. [#]†Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Table 13: Baseline disease characteristics (FAS and genotype-matched analysis set, MAA data cut-off 30th October 2020 and MAA safety update data cut-off 31st October 2021)

Parameter statistic	cPMP-treated patients (FAS and GMAS)			Untreated controls		
	MCD-501 only (N=4) †	MCD-201 (N=8)	MCD-202 only (N=3)	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Patients with early seizures [c]						
No symptoms reported	0	2 (25.0)	0	2 (14.3)	3 (8.1)	1 (5.3)
First Seizure in Utero or During Neonatal Period	4 (100)	5 (62.5)	2 (100)	11 (78.6)	26 (70.3)	13 (68.4)
First Seizure Post Neonatal Period	0	1 (12.5)	0	1 (7.1)	8 (21.6)	5 (26.3)
MoCD presenting signs and symptoms [d]						
Seizures	4 (100)	5 (62.5)	1 (33.3)	10 (71.4)	34 (91.9)	18 (94.7)
Feeding difficulties	4 (100)	4 (50.0)	1 (33.3)	9 (64.3)	31 (83.8)	17 (89.5)

Parameter statistic	cPMP-treated patients (FAS and GMAS)			Untreated controls		
	MCD-501 only (N=4) †	MCD-201 (N=8)	MCD-202 only (N=3)	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
High-pitched crying	3 (75.0)	4 (50.0)	0	7 (50.0)	16 (43.2)	10 (52.6)
Exaggerated startle response	2 (50.0)	3 (37.5)	0	5 (35.7)	12 (32.4)	9 (47.4)
Metabolic acidosis	2 (50.0)	2 (25.0)	0	4 (28.6)	7 (18.9)	4 (21.1)
Hypertonia	NA	3 (37.5)	0	3 (21.4)	NA	NA
Hypotonia	NA	2 (25.0)	0	2 (14.3)	NA	NA
Encephalopathy	NA	3 (37.5)	0	3 (21.4)	NA	NA
Intracranial haemorrhage	2 (50.0)	0	0	2 (14.3)	2 (5.4)	0
Other	2 (50.0)	5 (62.5)	0	7 (50.0)	11 (29.7)	5 (26.3)

Source: EMA D166 update (2022). Note: Hypertonia, hypotonia, and encephalopathy were not collected as signs/symptoms in the MCD-501 and MCD-502 studies. [c] Early seizures are defined as those reported either while the patient was *in utero* or within the first 28 days of life. [d] No prespecified signs and symptoms were reported for one patient in study MCD-202. †Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Parental consanguinity was reported in seven of the 14 treated patients (50%) and 25 of the 37 untreated controls (67.6%). 8 of the treated patients had a total of 15 living siblings, of which one had confirmed MoCD Type A. 7 treated patients had a total of ten deceased siblings, of which five had confirmed MoCD Type A status and three were suspected of having MoCD Type A. The number of living or deceased siblings along with their MoCD Type A status was unavailable for untreated control patients.

At the data cut-off of 31st October 2021, MoCD family history was similar in the FAS and GMAS untreated population.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analysis

Analysis of the individual studies was exploratory in nature. Pivotal efficacy evidence was derived from the integrated efficacy analysis: described below are the methods for the most important efficacy parameters. A summary of the statistical analysis of the integrated efficacy analysis is displayed in Table 14.

Table 14: Summary of statistical analyses

	Integrated summary of efficacy (ISE)
Hypothesis and objectives	The objective of the ISE was to summarise the clinical efficacy data for cPMP (inclusive of both rcPMP and ORGN001) and provide an analysis that allows an interpretation of the response to cPMP in the target population – neonate and paediatric patients with MoCD Type A – and to compare this response to the course of the disease in comparable patients that took part in the natural history study. The key efficacy objectives in the integrated summary were to evaluate overall survival and to assess select biomarkers, feeding patterns, growth parameters, gross motor function and developmental assessments, and seizures of patients treated with cPMP with MoCD Type A compared to untreated patients in the natural history study. Neurologic examinations and neuroimaging assessments were also considered.
Statistical analysis	Three analysis populations were constructed: • FAS: All patients with MoCD Type A. This population includes all treated and untreated MoCD Type A patients. • Prospective FAS (PFAS): All patients with MoCD Type A were followed prospectively in studies MCD-502, MCD-201, and MCD-202. This population is a subset of the FAS. • GMAS: All patients with MoCD Type A included in the m:n matching (where m is the number of treated patients and n is the number of natural history controls in a given match). The FAS serves as the primary analysis set for conducting the efficacy analyses, while the PFAS and GMAS are supportive analysis populations. Please see below for more information.
Interim analysis and stopping guidelines	No stopping guidelines or interim analysis was prespecified.
Sample size, power calculation	No formal sample size calculations were performed.
Data management, patient withdrawals	In the integrated clinical efficacy datasets, patients were identified using a unique combination of protocol number, site number, and patient number. For the six patients treated under protocol MCD-501 and subsequently enrolled under protocol MCD-201, a single unique subject identifier was used for all assessments. Similarly, for patients enrolled in a) both MCD-501 and MCD-503 or b) both MCD-502 and MCD-503, a single unique subject identifier was used. Regarding handling of dropouts or missing data, missing data for efficacy assessments was managed as specified in the instructions for each instrument, as applicable. If a date of a measurement or an event had a missing or an unknown day, the missing or unknown day was substituted by 15 for the calculation of variables such as age at which the measurement was taken or the age at the occurrence of an event. If the month or the year of a date was missing, no imputation took place. No other missing dates were imputed. Regarding baseline definitions, two distinct definitions of baseline were used for change from baseline type analyses: • True baseline, defined as the last known measurement prior to or on the date of the first cPMP dose for those patients who were treated with cPMP; or the first measurement prior to prospective data collection for patients in the natural history study. • First value, defined as the measurement with the earliest date of collection, for all patients. True baseline served as the primary reference point, whereas the first value served as a supportive reference point.

	Concerning visit windows, two sets of analysis visits were derived, one using true baseline as a reference and one using the first value as a reference.

Source: ISE Statistical Analysis Plan (SAP).(52) Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=full analysis set; GMAS=genotype-matched analysis set; ISE=Integrated Summary of Efficacy; m:n=number of treated patients:natural history controls in a given match; MoCD Type A=molybdenum cofactor deficiency Type A; PFAS=prospective full analysis set.

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

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

The FAS serves as the primary analysis set for conducting the efficacy analyses, while the PFAS and GMAS are supportive analysis populations.(34-37)

Genotype matching

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

The following approach was used to determine matching:

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

The protein products of *MOCS1*, *MOCS1*A and *MOCS1*B contain sites and regions with highly conserved amino acids across all cellular life, from single-celled bacteria to humans (53). Only a small group of proteins are currently known to have this high level of conservation, with nearly all being intimately connected to sustaining life. In discussions with researchers who provided much of the published data on protein structure, the sponsor matched treated patients to natural history control patients based on the mutations' known impact on either *MOCS1A* or *MOCS1B*.

The matching criteria are appropriate and informs on the efficacy of cPMP. This is because key baseline characteristics of the patients are comparable, thus supporting the matching algorithm across treated and untreated patients:(34-37)

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

Efficacy analyses

Overall survival

The first efficacy outcome measure is overall survival. Overall survival (OS) is defined as the interval in months from the date of birth to the date of death or date last known alive (patients still on the study are censored at the data cut-off, and

patients alive at the last contact date are censored as well), whichever occurs first.(34-37)

Genotype-matched overall survival analysis

Unadjusted analysis

OS is analysed using the GMAS population via Kaplan-Meier methods. Survival curves of treated and natural history controls are provided, as well as curves by symptom onset and treatment initiation subgroups. Cox proportional hazard models are also fitted using the GMAS. No form of adjustment for genotype matching is used.(34-37)

Adjusted analysis by matched ID

OS is analysed using the GMAS population using Kaplan-Meier methods, stratified by matched ID. The stratified log-rank test is used to compare median survival between treated and natural history controls while controlling for the genotype-matched IDs. Additional analyses following the Kaplan-Meier methods are performed. A Cox proportional hazards model is also fitted to assess the treatment effect on OS.(34-37)

Inversely weighted analysis

The average treatment effect (ATE) is estimated based on the GMAS population via the Cox proportional hazards model that accounts for the clustering within strata (matched IDs) and incorporates the appropriate set of weights. These ATE weights are defined post-matching to determine the effect of treatment on the hazard of the occurrence of death in the GMAS. The ATE weights are described in the SAP.(34-37)

Analysis of biomarkers

Biomarkers analysed include MoCD-associated urine and plasma biomarker levels consisting of s-sulphocysteine (SSC), xanthine, and uric acid. Levels of biochemical markers measured in urine are normalised to urine creatinine levels. The actual value over time is presented via summary tabulations and graphical representations. Analysis of biomarkers is presented using the FAS and the GMAS.(34-37)

Feeding patterns

Feeding patterns are analysed via the frequency and percentages of each feeding method at the last visit where the feeding pattern was recorded. In addition, feeding methods are tabulated dichotomously using the last recorded feeding pattern, categorised as oral vs non-oral. The age (in months) at the last feeding assessment is summarised using descriptive statistics.

The dichotomous analysis is performed using logistic regression, with oral feeding (yes/no) as the dependent variable, and treatment status (yes/no), an indicator for the MoCD symptom onset subgroup, age (months) at the last feeding assessment, and gender as independent variables. Odds ratios and 95% confidence intervals are provided. The analysis of feeding patterns is performed on the FAS and the GMAS population. A conditional logistic regression model is fitted to investigate the relationship between feeding patterns and treatment status.(34-37)

Growth parameters

Various growth parameters (such as body weight, length, head circumference, and body mass index [BMI]) in the FAS and patient subgroups are converted to age-adjusted z-scores and percentiles. Descriptive statistics were provided for each parameter over time and changes from baseline. Standard growth curves from WHO are used for children up to 5 years old, and Centers for Disease Control and Prevention (CDC) growth charts are used for older children. Individual and aggregate patient plots are presented for percentiles and z-scores.(34-37)

Gross motor function

Results from the Gross Motor Function Classification System Extended and Revised (GMFCS-ER) are tabulated for the FAS, Partial FAS (PFAS), and patient subgroups. Data is summarised over time for each GMFCS level, and dichotomous results are also presented for Levels I to IV versus Level V. Bar charts display frequency trends over time and for treated versus natural history controls.(34-37)

Developmental assessments

Bayley and WPPSI data for motor and cognitive subtests using age-equivalent scores and developmental quotient scores are presented graphically. This analysis was conducted for PFAS patients with limited retrospective data. Data on the number of patients who could sit independently for 30 seconds at 12 months and at any time is also provided.(34-37)

Seizures

Seizure analysis is performed for the FAS, PFAS, and patient subgroups. Patients are categorised based on seizure history: 'never had seizures,' 'had seizures but resolved,' 'had seizures controlled with medication,' or 'still having seizures regularly.' A proportional odds model is used to analyse these categories, considering treatment status, age at assessment, MoCD symptom onset subgroup, and gender as independent variables.(34-37)

Neurologic examinations and Neuroimaging:

The frequency and percentages of patients with neurologic examination findings and normal/abnormal neuroimaging results over time for the FAS, PFAS, and GMAS are presented, including patient subgroups. Note that reporting methods regarding the classification of abnormal neuroimaging results differed between studies.(34-37)

B.2.4.2 Patient disposition

Table 15 summarises the disposition status of the 52 patients included in the integrated analyse. All 52 patients had a confirmed diagnosis of MoCD Type A. Overall, 15 patients who received cPMP were included in the treated patient group and 37 patients from the natural history study were included in the untreated control group.(49)

As of the MAA update data cut-off of 31st October 2021, 10 of the 15 (66.7%) treated patients were ongoing on cPMP, including eight patients in study MCD-201 and two patients in study MCD-202. Overall, 5 of the 15 treated patients discontinued treatment. One treated patient, from study MCD-202, was discontinued from the study after nine days (and nine doses of cPMP), per a physician decision related to the poor neurologic prognosis of the patient. Of the remaining discontinued patients, who all participated in study MCD-501, two died and two were reported as off treatment (due to ‘abnormal imaging’ or ‘poor neurologic prognosis’).(49)

The FAS includes all 52 patients: 15 treated and 37 untreated controls. The PFAS includes 25 patients overall: 11 patients with prospective data collected during treatment with cPMP in studies MCD-201 and MCD-202 and 14 patients from the natural history study MCD-502 who had prospective data collected. The 15 treated patients were matched based on genetic mutation to 19 untreated control patients;l

these 34 patients comprise the GMAS. Of note is that one patient was enrolled in study MCD-202 during the D90 update period, meaning they are included in the FAS/PFAS and GMAS, but their data was not included in all endpoint analyses.(49)

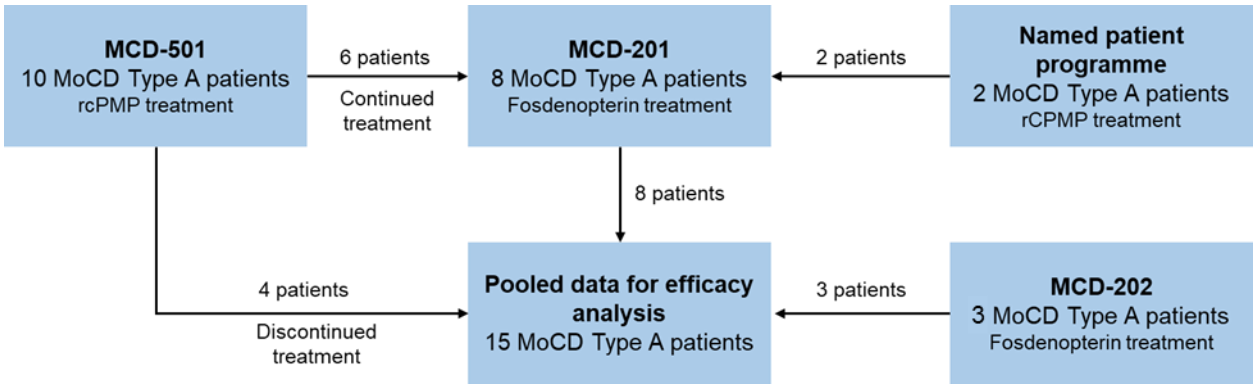
Table 15: Patient disposition and summary of integrated analysis sets (MAA safety update data cut-off: 31st October 2021)

Disposition category	cPMP-treated patients				Untreated controls
	MCD-501 only (N=4) † n (%)	MCD-201 (N=8) n (%)	MCD-202 only (N=3) n (%)	Total (N=15) n (%)	MCD-502 (N=37) n (%)
Number of patients included	4	8	3	15	37
Number of patients ongoing as of data cut-off	0	8 (100)	2 (50.0)	10 (64.3)	0
Number of patients off treatment	4 (100)	0	1 (50.0)	5 (35.7)	37 (100)
Number of patients with follow-up information from study MCD-503[a]	0	NA	NA	0	6 (16.2)
FAS	4 (100)	8 (100)	3 (100)	15 (100)	37 (100)
PFAS	0	8 (100)	3 (100)	11 (71.4)	14 (37.8)
GMAS	4 (100)	8 (100)	3 (100)	15 (100)	19 (51.4)

Source: EMA D166 update (2022). Abbreviations: cPMP=cyclic pyranopterin monophosphate; NA=not applicable=rcPMP, recombinant cyclic pyranopterin monophosphate. †Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

The participant flow diagram is provided in Figure 9.

Figure 9: Participant flow in the integrated efficacy analysis



Abbreviations: MoCD = molybdenum cofactor deficiency; rcPMP = recombinant cyclic pyranopterin monophosphate.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The complete quality assessment for each study is provided in Appendix D.1.

All SLR methods come with inherent limitations. The data synthesised in an SLR is contingent on the quality and quantity of information available during the search. It is important to note that any studies published after the search date will not have been included, meaning an updated search may be required in the future. Moreover, publication bias can further exacerbate the impact of findings in an SLR. Studies with positive results are more likely to be published, while those with negative or null results may be overlooked or remain unpublished. As a result, the synthesised data in this SLR may be skewed towards studies that show significant effects, leading to an overestimation of intervention efficacy or effect size.

The main limitation of the SLR is the sparsity of the evidence identified, with most included studies being case reports or series. Case reports and series lack the methodological rigour of other study designs, such as randomised controlled trials, and may contain incomplete or inaccurate information. Relying solely on case reports can limit the synthesised evidence's quality and reliability. Furthermore, case reports cannot establish causality due to the lack of a control group or comparison with other similar cases. This makes it difficult to draw definitive conclusions about the causal relationship between exposures and outcomes. Nevertheless, there was consensus among the identified studies that treatment with cPMP, when initiated early, can significantly improve outcomes and symptomology in patients with MoCD Type A.

The rarity of MoCD Type A also means there is a possibility that individuals may be double-counted – that is, that the same patient could appear in multiple studies and not be identified as such due to anonymous reporting.

B.2.6 Clinical effectiveness results of the relevant studies

Since the pivotal evidence comes from the integrated efficacy analysis from studies MCD-501, MCD-201, MCD-202 and natural history studies MCD-502 and MCD-503, integrated efficacy data will be presented instead of the individual results of the studies.

B.2.6.1 Overall survival

Treatment of patients with MoCD Type A with cPMP led to a statistically significant improvement in OS compared with the untreated control patient population, in both the FAS and GMAS (Table 16).(49)

As of the data cut-off date of 31st October 2021, 2 of the 15 treated patients (13.3%) and 24 of 37 untreated control patients (64.9%) in the FAS had died. Median OS was not estimated for the treated patient group given the low number of patient deaths; it was 50.7 months (4.2 years) for the untreated control group (log-rank p=0.0091). The rate of death among the untreated control group was 5.5 times higher than that of the treated patient group. Consistent with these results, the survival probability at 1 year of age was 93.3% for the treated group and 75.3% for the untreated controls; at 2 and 3 years of age, survival probabilities were 85.5% and 85.5% for treated patients and 69.6% and 55.1% for untreated control patients, respectively (49).

The Kaplan-Meier curves of OS for the treated and untreated patients included in the FAS are presented in Figure 9.(49)

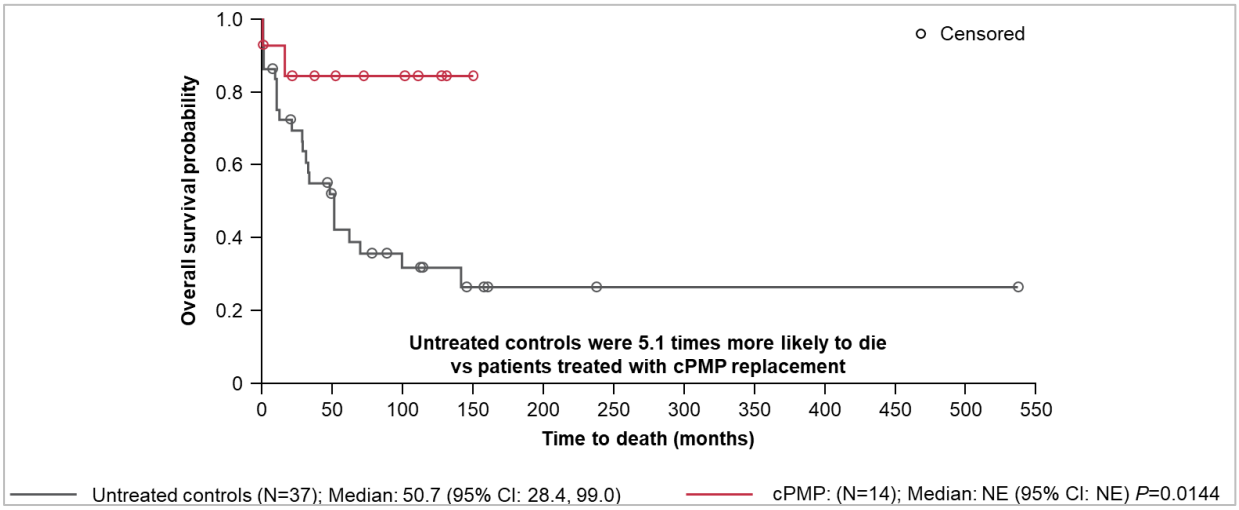
Table 16: Overall survival (FAS, data cut-off 31 Oct 2021)

Parameter statistic	**cPMP-treated patients**				**Untreated controls**
	MCD-501 only (n=4)	MCD-201 (n=8)	MCD-202 (n=3)	Total (n=15)	MCD-502 (n=37)
Patients censored, n (%)	2 (50.0)	8 (100)	3 (100)	13 (86.7)	13 (35.1)
Reason for censoring					
Data cut-off, n (%)	0	8 (100)	2 (66.7)	10 (66.7)	0
Alive at last contact	2 (50.0)	0	1 (33.3)	3 (20)	13 (35.1)
Deaths, n (%)	2 (50.0)	0	0	2 (13.3)	24 (64.9)
Time to death (months)					

Parameter statistic	cPMP-treated patients				Untreated controls
	MCD-501 only (n=4)	MCD-201 (n=8)	MCD-202 (n=3)	Total (n=15)	MCD-502 (n=37)
75th percentile (95% CI)[a]	-	-	-	NE (NE)	NE (61.7, NE)
Median (95% CI)[a]	-	-	-	NE (NE)	50.7 (28.4, 99.0)
25th percentile (95% CI)[a]	-	-	-	NE (0.2, NE)	12.1 (1.0, 31.2)
Min, max	-	-	-	0.2, 15.9	0.3, 141.1
Log-rank p-value	-	-	-		0.0091
Cox PH model Hazard ratio (95% CI) [b]	-	-	-		5.5 (1.44, 21.04)
Kaplan-Meier survival probability[c]					
6 months, (%)	-	-	-	0.9333	0.8649
1 year, (%)	-	-	-	0.9333	0.7533
2 years, (%)	-	-	-	0.8556	0.6964
3 years, (%)	-	-	-	0.8556	0.5513

Source: EMA D166 update (2022). [a] Quartile estimates from product-limit (Kaplan-Meier) method, with associated log-log CIs. [b] Cox proportional hazards model regressing survival status on an indicator variable denoting treatment status. Hazard ratios are estimated to determine the effect of treatment on the hazard of the occurrence of death. The 95% CIs are based on the modified score test statistic under the Cox model. The hazard ratio represents the risk of death in the natural history patients compared to the treated patients. [c] Based on survival distribution function estimates from the product-limit method. †Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201. (49)

Figure 10: Kaplan-Meier plot of OS for cPMP-treated patients and untreated controls (FAS, data cut-off 31st October 2021)



Source: EMA D166 update (2022). Abbreviations: CI=confidence interval; cPMP=cyclic pyranopterin monophosphate; NE=not estimated.(49)

Results in the GMAS were consistent with the FAS. As of the data cut-off date of 31st October 2021, 2 of the 15 treated patients (13.3%) and 14 of 19 untreated matched control patients (73.7%) in the GMAS had died. Median OS was not estimated for the treated patients; it was 47.8 months (3.9 years) for the untreated matched controls (log-rank p=0.0028, unadjusted). Patients in the untreated control group were 7.1 times more likely to have died than patients who received cPMP. Consistent with these results, the survival probability at 1 year of age was 93.3% for the treated group and 68.4% for the untreated controls. At 2 years of age, survival probabilities were 85.5% and 63.2% for treated and untreated matched control patients, respectively.(49)

B.2.6.2 MoCD urine biomarkers

Treatment with cPMP led to a rapid reduction in levels of the MoCD-associated urinary biomarkers of SSC and xanthine normalised to creatinine and an increase in urinary uric acid normalised to creatinine; these improvements were maintained over long-term treatment with cPMP. In the untreated control group, levels of normalised urinary SSC and xanthine remained elevated over time and levels of normalised urinary uric acid remained low. At first value, mean levels of urinary SSC normalised to creatinine were elevated and similar between treated (166.3 µmol/mmol) and untreated patients (136.3 µmol/mmol).(49)

Treatment with cPMP led to a rapid reduction in the levels of urinary SSC normalised to creatinine to a mean of 64.1 µmol/mmol on Day 2. At Month 3, mean levels of urinary SSC normalised to creatinine were further reduced to 12.3 µmol/mmol in treated patients, and remained elevated at 159.6 µmol/mmol in untreated patients. At the last visit, mean levels of urinary SSC normalised to creatinine were 8.6 µmol/mmol in treated patients and 156.6 µmol/mmol in untreated patients, representing a mean reduction from the first value of -157.7 µmol/mmol in treated patients and a mean increase of 24.8 µmol/mmol in untreated controls.(49)

Similar to what was observed for urinary SSC normalised to creatinine, mean levels of urinary xanthine normalised to creatinine at first value were similar between treated (241.8 µmol/mmol) and untreated patients (315.8 µmol/mmol). Treatment with cPMP led to a rapid reduction in the levels of urinary xanthine normalised to creatinine to a mean of 142.1 µmol/mmol on Day 2. At Month 3, mean levels of

urinary xanthine normalised to creatinine were further reduced to 28.8 µmol/mmol in treated patients and remained elevated at 558.4 µmol/mmol in untreated controls. At the last visit, mean levels of urinary xanthine normalised to creatinine were 17.9 µmol/mmol in treated patients and 338.2 µmol/mmol in untreated patients, representing a mean reduction from first value of -223.9 µmol/mmol in treated patients and a mean increase of 28.6 µmol/mmol in untreated controls. Uric acid concentrations are typically decreased in patients with MoCD Type A.(49)

The mean level of urinary uric acid normalised to creatinine at first value was 428.8 µmol/mmol; this value is reflective of maternal levels, as most of the cPMP-treated patients had the first assessment conducted in the early neonatal period. In the untreated control patients, the mean level of urinary uric acid normalised to creatinine at first value was low, at 99.1 µmol/mmol (pathologic range <100 µmol/mmol). Treatment with cPMP was associated with an increase in the concentration of urinary uric acid normalised to creatinine. At Month 3, the mean level of urinary uric acid normalised to creatinine was 692.2 µmol/mmol in treated patients and remained as low as 40.7 µmol/mmol in untreated patients. At the last visit, the mean level of urinary uric acid normalised to creatinine was 506.4 µmol/mmol in treated patients and 45.0 µmol/mmol in untreated patients, representing a mean increase of 77.6 µmol/mmol in treated patients and a mean reduction of -67.7 µmol/mmol in untreated controls (49). **Error! Reference source not found.**, [redacted], and [redacted] present box plots of observed values for urinary SSC, xanthine, and uric acid normalised to creatinine over time, respectively.(49)

[redacted]

B.2.6.3 Feeding patterns

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

In the FAS, 8 of the 14 treated patients (57.1%) and ten of the 33 untreated patients (30.3%) with data available for analysis were able to feed orally at the last recorded visit. The odds ratio indicates that treated patients were 7.8 times more likely to be fed orally at the last assessment compared with patients in the untreated control group (Table 17).

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

Results in the GMAS were consistent with the FAS. For this matched population, only 4 (22.2%) of 18 untreated patients with data available were able to feed orally at the last assessment. In this population, treated patients were 9.1 times more likely to be feeding orally at the last assessment than the untreated matched controls. Results of the conditional logistic regression analysis of feeding patterns for the GMAS were consistent, indicating that treated patients were more likely to be feeding orally at the last assessment with a hazard ratio of 4.2. The median time to sustained non-oral feeding for the untreated matched control patients in the GMAS was 5.7 months, compared with 75.0 months in treated patients.

Table 17: Analysis of feeding status at last assessment and time to sustained non-oral feeding (FAS and GMAS, data cut-off 31st October 2020)

Parameter statistic	**cPMP-treated patients (FAS and GMAS) (N=14)**	**Untreated controls**	
		MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Number of patients with last feeding assessment, n	14	33	18
Number of patients feeding orally, n (%)	8 (57.1)	10 (30.3)	4 (22.2)

Parameter statistic	cPMP-treated patients (FAS and GMAS) (N=14)	Untreated controls	
		MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Number of patients not feeding orally, n (%)	6 (42.9)	23 (69.7)	14 (77.8)
Logistic regression [a]			
Odds ratio (95% CI)	7.8 (1.38, 43.84)		9.1 (1.16, 72.39)
p-value	0.020		0.036
Time to non-oral feeding (months)			
75th percentile (95% CI)	NE (75.0, NE)	100.8 (19.2, NE)	53.6 (6.5, NE)
Median (95% CI)	75.0 (14.4, NE)	10.5 (4.9, 53.6)	5.7 (0.2, 22.5)
25th percentile (95% CI)	14.5 (0.0, 75.0)	0.6 (0.1, 6.5)	0.2 (0.1, 1.7)
Min, max	0.0, 75.0	0.1, 100.8	0.1, 53.6

Source: EMA D166 update (2022). Note: Sustained non-oral feeding is defined as the time at which the patient never subsequently returns to an oral method of feeding. [a] The logistic regression is fitted using oral feeding (yes/no) as the dependent variable, and treatment status, MoCD symptom onset subgroup, age at last feeding assessment, and gender as independent variables. The odds ratio represents the odds of feeding orally when being treated versus not being treated.(49)

B.2.6.4 Growth parameters

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

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

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

Table 18: Summary of first value and last assessment for weight, height, and head circumference z-scores (FAS and GMAS, MAA data cut-off 31st October 2020)

Parameter visit statistic	cPMP-treated patients (FAS and GMAS)				Untreated controls	
	MCD-501 only (N=4) †	MCD-201 (N=8)	MCD-202 (N=2)	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Weight z-score						

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

Source: EMA D166 update (2022). First value is defined as the measurement with the earliest date of collection. (34-37); † Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

B.2.6.5 Developmental assessments

Data on developmental assessments is presented for the 14 early-onset patients.

Gross Motor Function Classification System results

Children who have motor functions classified at Level I on the GMFCS-ER scale can generally walk without restrictions. Children whose motor function has been classified at Level V are very limited in their ability to move themselves around even with the use of assistive technology and typically are pushed in a wheelchair.

Note that GMFCS-ER was only captured during the prospective studies MCD-201 and MCD-202 and in the prospective part of MCD-502. Table 19 provides GMFCS-ER level at the last available assessment for the PFAS. Data was available for 8 of 10 patients during treatment with cPMP and for 11 of the 14 untreated controls included in the PFAS.(49)

At baseline, four of the nine treated patients were rated as Level I, 1 as Level IV and four as Level V. In the untreated control group, 1 was rated as Level I, 1 as Level II and nine as Level V.

At the last assessment prior to the MAA data cut-off, a higher percentage of patients receiving cPMP who had data available were ambulatory (4/9, 44.4%) (i.e., assessed as a Level I on the GMFCS-ER) compared with untreated controls (1/11, 9.1%). One additional treated patient was walking with assistance at 4 years old and was rated as a Level III on the GMFCS-ER. The majority of the untreated control patients (9/11, 81.8%) required transportation in a wheelchair for mobility (Level V). In the treated patient group, 4 of the nine patients (44.4%), all of whom entered study MCD-201 with static encephalopathy and at GMFCS-ER Level V, were assessed as Level V at the last assessment (49).

In the GMAS, all seven (100%) of the matched control patients with data available were non-ambulatory (Level V) (49).

Table 19: GMFCS results at the last assessment (PFAS, data cut-off 31st October 2020)

Analysis visit result	cPMP-treated patients (N=10) n (%)	Untreated controls (N=14) n (%)
Data Availability	9 [a]	11
Level I, II, III, and IV	5 (55.6)	2 (18.2)
Level I	4 (44.4)	1 (9.1)
Level II	0	0
Level III	1 (11.1)	0
Level IV	0	1 (9.1)

Analysis visit result	cPMP-treated patients (N=10) n (%)	Untreated controls (N=14) n (%)
Level V	4 (44.4)	9 (81.8)

Source: EMA D166 update (2022). Abbreviations: cPMP=cyclic pyranopterin monophosphate. [a] N=10 as no developmental data were available for one patient.(49)

One patient was assessed on the Gross Motor Function Measure (GMFM-88) at 34.3 months of age and 35.8 months of age, with total percent scores of 78% and 70.2%, respectively. Per protocol, the Gross Motor Function Classification System – Expanded and Revised (GMFCS-ER) was not administered by the last assessment before the data cut-off; however, based on the patient's functioning level at 35.8 months of age (ability to walk independently without an assistive device and run with coordination), the patient would be rated Level I on the GMFCS-ER (49).

Bayley and WPPSI

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

The Bayley assesses the developmental functioning of infants and children 1 month to 42 months of age and consists of the following scales: Cognitive; Language (administered only to native English speakers in English speaking countries), which includes Receptive and Expressive Communication subtests; and Motor, which includes Fine and Gross motor subtests. The WPPSI measures cognitive skills in children aged 30 months to 7 years, 7 months, using 14 different subtests which examine cognitive function aspects such as vocabulary, visual spatial skills, logic, processing speed, and memory.

The higher functioning patients in all areas received treatment with cPMP; all untreated controls were lower functioning for all Bayley assessments. All the treated patients with lower age-equivalent scores had entered study MCD-201 with static encephalopathy. These four patients had age-equivalent scores that generally remained stable during treatment with cPMP, with some gaining new skills. A summary of the cognitive developmental assessments for baseline and last assessment (when available) for the GMAS by matched ID is presented in Table 20. The table presents all patients in the GMAS with available data, regardless of the availability of data from a matched patient.

For the treated patients, data are available from the start of cPMP and are consistent with the data presented in the figures above; the four patients who entered study MCD-201 without static encephalopathy who were higher functioning at study entry showed improvement during treatment with cPMP as did the patient who was treated with cPMP in study MCD-202.(49) One patient, enrolled during the update period, was assessed using the Bayley Scales of Infant and Toddler Development Third Edition (Bayley) at 34.3 months of age and 35.8 months of age. Language scale assessments were not performed as the patient was non-English speaking. At 34.3 months of age, the patient had age-equivalent scores of 25 months in the cognitive subtest, 32 months in the fine motor subtest, and 26 months in the gross motor subtest. The patient age-equivalent score on the cognitive subtest improved to 32 months at the last available assessment at 35.8 months of age.(49)

Table 20: Summary of cognitive developmental assessments by matched ID (GMAS data cut-off 31st October 2020)

Matched ID	Treated/untreated	Age at first visit/age at last visit	Age-equivalent	
			First visit	Last visit
1	Treated	6.3 years/11.8 years	3.0 months	4.7 months
2	Treated	4.9 years/9.9 years	30.0 months	3.8-5.8 years[a]
	Treated	5.1 years/9.1 years	0.5 months	2.0 months
3	Treated	5.1 years/10.3 years	4.0-5.0 years[a]	4.9-7.6 years[a]
4	Treated	3.8 years/9.1 years	26.0 months	33.0 months
	Untreated	8.0 years/9.1 years	2.3 months	2.0 months
5	Treated	7.8 months/5.7 years	3.3 months	2.7 months
	Untreated	3.3 years/4.1 years	0.5 months	0.5 months
6	Treated	28 days/4.0 years	0.5 months	20.0 months
8	Untreated	4.0 years	0.5 months	No other assessments
	Untreated	4.0 years	0.5 months	No other assessments
9	Treated	23 months/8.4 years	1.3 months	2.3 months
	Untreated	8.7 years/9.1 years	2.3 months	2.3 months
11	Treated	29.4 months/35.5 months	21.0 months	25.0 months

Source: EMA D166 update (2022).(49)

Unassisted sitting

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

Treated patients were more likely to be able to sit unassisted than the untreated controls at 12 months of age and at any time. By 12 months of age, 3 of the seven treated patients (42.9%) with data available were able to sit unassisted for 30 seconds, compared with three of the 27 untreated control patients (11.1%). The ability to sit unassisted at any time was reported for six of the nine treated patients (66.7%) and three of the 27 untreated controls (11.1%) in the FAS for whom data was available; none of the matched control patients in the GMAS could sit unassisted at any time.(49)

Table 21: Analysis of unassisted sitting (FAS and GMAS, MAA data cut-off 31 October 2020)

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

Source: EMA D166 update (2022). Note: Patients were only included in the analysis of unassisted sitting if they had at least one assessment on or after 9 months of age. Note: For treated patients, results are based on the Developmental Milestones Module of the Denver Scale, or the Bayley Gross Motor Subscale Question #26. Those that do not have this question answered but had higher Bayley gross motor subscale questions answered positively at 12 months were assumed to have been able to sit independently for 30 seconds at 12 months. For patients in MCD-502 results are based on the corresponding question from the neurological examination. †Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Seizures

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

Consistent with the disease, most patients in the natural history control group had seizures that were either controlled or ongoing (present) on AED therapy. Among treated patients, 7 of the 14 patients (50.0%) had seizures ongoing and 2 (14.3%) had seizures controlled on AEDs. In the untreated control group, 13 of 37 patients (35.1%) had seizures ongoing, and 20 patients (54.1%) had seizures controlled. Very few patients did not have seizures present at any time: 2 of 14 treated patients (14.3%) and 3 of 37 (8.1%) were untreated patients. Importantly, three of the 14 treated patients (24.1%) had seizures resolved while treated with cPMP, compared with one of the 37 untreated controls (2.7%).

The incidence of seizures was similar in the GMAS. 8 of the 19 untreated patients (42.1%) had seizures ongoing at the last visit, with ten patients (52.6%) having their seizures controlled and no patients having seizures resolved.

Odds ratios displayed apparent difference between the treated patients and untreated controls for the likelihood of having seizures not present or resolved versus having seizures controlled or continuing (present) in the FAS or GMAS. Results were consistent based on the adjusted model for the GMAS.

Table 22: Seizure status at last assessment (FAS and GMAS)

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

Source: EMA D166 update (2022). Note: Seizure status is derived based on the last date of contact.a A proportional odds model is fitted based on the cumulative logit function, with seizure status as dependent variable and treatment status, MoCD symptom onset, and gender as independent variables. The odds ratio represents the odds of the treated patients to have seizure status as either Not Present or Resolved versus Controlled or

Present, compared to the natural history patients. † Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

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

The number and types of prior and concomitant AEDs reported in the GMAS were similar to those reported in the FAS. One patient had no history of seizures. This patient did not experience seizures during the observation period from 32.7 months of age to 3.3 years of age, and no AEDs were administered. Results of an electroencephalogram performed at screening (32.7 months of age) were normal.

Table 23: Summary of prior and concomitant antiseizure medication reported in two or more patients by WHO ATC class (FAS, MAA data cut-off 31 October 2020)

WHO ATC class	cPMP-treated patients (FAS and GMAS)				Untreated controls	
	MCD-501 only (N=4) † n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)	Total (N=14) n (%)	MCD-502 FAS (N=37) n (%)	MCD-502 GMAS (N=19) n (%)
Patients with at least one antiseizure medication	4 (100.0)	4 (50.0)	2 (100.0)	10 (71.4)	31 (83.8)	17 (89.5)
Antiepileptics/barbiturates and derivatives	4 (100.0)	1 (12.5)	2 (100.0)	7 (50.0)	31 (83.8)	17 (89.5)
Psycholeptics	2 (50.0)	0	0	2 (14.3)	12 (32.4)	6 (31.6)
Benzodiazepine derivatives	0	4 (50.0)	0	4 (28.6)	0	0
Fatty acid derivatives	0	2 (25.0)	0	2 (14.3)	0	0
Other antiepileptics	0	3 (37.5)	0	4 (28.6)	0	0

Source: EMA D166 update (2022). †Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Neuroimaging

A summary of first and last status reported for neuroimaging in the FAS is presented in Table 24. Note that there are differences between the studies with regards to reporting of normal and abnormal results: MCD-201 and -202 reported results as 'normal', 'abnormal not clinically significant', or 'abnormal clinically significant', whereas in MCD-501 and MCD-502 results were only reported as 'normal' or 'abnormal'. By-patient results for the first and last neuroimaging assessments describing the abnormalities reported for the GMAS by matched ID are summarised in Table 24.(49)

As expected, based on the MoCD Type A phenotype, most patients in both the treated and untreated groups had abnormal neuroimaging results. Furthermore, the majority of patients who completed the neuroimaging assessments experienced no change in findings. One patient who received both rcPMP and cPMP had an improvement reported from 'abnormal, clinically significant' at the first assessment in study MCD-201 to 'abnormal, not clinically significant' at 0.6 years later. Their MRI results continued to be reported as not clinically significant through the last assessment.(49)

Among patients in the untreated control group, 33 (89.2%) of the 37 patients had abnormal results at the first assessment, with consistent results reported at the last assessment (35 patients, 94.6%). Results were similar for the 19 matched control patients in the GMAS, with 17 of 19 patients (89.5%) having abnormal results at the last assessment. The neuroimaging results reported in the PFAS were similar to those reported in the FAS. For one patient, an MRI performed at screening (32.7 months of age) was abnormal, not clinically significant, and showed abnormal basal ganglia. No other imaging assessments were performed (49).

Table 24: Summary of neuroimaging results (FAS and GMAS, data cut-off 31st October 2020)

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

Source: EMA D166 update (2022). [a] This patient had two neuroimaging assessments *in utero*, including an ultrasound that was reported as normal (as reflected in the table) and an MRI conducted ~3 weeks prior to birth that showed cerebral dysgenesis. †Six out of the eight patients who participated in study MCD-501 also

participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Neurologic examinations

Overall, cPMP-treated patients had better neurological functioning at the last visit compared with untreated controls. Results for data collected prospectively for neurologic examinations are summarised in Table 25.(49)

Compared to untreated patients, a lower percentage of patients (FAS analysis) receiving cPMP treatment had abnormal results at the last assessment for truncal tone (50.0% treated vs 89.2% untreated), appendicular tone (57.1% treated vs 94.6% untreated), and deep tendon reflexes (64.3% treated vs 81.1% untreated) (49).

The neurologic examination results reported in the PFAS were similar. At last visit, cPMP-treated patients had better neurological functioning compared with untreated control patients, with a lower percentage of patients reporting abnormal results for spontaneous movement (60.0% treated vs 92.9% untreated), truncal tone (70.0% treated vs 92.9% untreated), appendicular tone (80.0% treated vs 100% untreated), and deep tendon reflexes (70.0% treated vs 92.9% untreated). For one patient, results from neurologic examinations performed at screening (32.7 months of age) were normal and remained unchanged up to the last available assessment at 3.3 years of age.(49)

Table 25: Summary of neurologic examination results at the last assessment (FAS and GMAS, data cut-off 31st October 2020)

Parameter result	**cPMP-treated patients**				**Untreated controls**	
	MCD-501 only (n=4) n (%)	MCD-201 (n=8) n (%)	MCD-202 (n=2) n (%)	Total (n=14) n (%)	MCD-502 FAS (n=37) n (%)	MCD-502 GMAS (n=19) n (%)
Spontaneous movement						
Normal	2 (50.0)	3 (37.5)	0	5 (35.7)	5 (13.5)	2 (10.5)
Abnormal	2 (50.0)	5 (62.5)	1 (50.0)	8 (57.1)	29 (78.4)	15 (78.9)
Not examined	0	0	1 (50.0)	1 (7.1)	0	0
Truncal tone						
Normal	0	2 (25.0)	1 (50.0)	3 (21.4)	3 (8.1)	1 (5.3)
Abnormal	0	6 (75.0)	1 (50.0)	7 (50.0)	33 (89.2)	17 (89.5)
Not examined	0	0	0	0	0	0
Appendicular tone						

Parameter result	cPMP-treated patients				Untreated controls	
	MCD-501 only (n=4) n (%)	MCD-201 (n=8) n (%)	MCD-202 (n=2) n (%)	Total (n=14) n (%)	MCD-502 FAS (n=37) n (%)	MCD-502 GMAS (n=19) n (%)
Normal	0	0	1 (50.0)	1 (7.1)	1 (2.7)	1 (5.3)
Abnormal	0	8 (100)	0	8 (57.1)	35 (94.6)	17 (89.5)
Not examined	0	0	1 (50.0)	1 (7.1)	0	0
Deep tendon reflexes						
Normal	2 (50.0)	2 (25.0)	1 (50.0)	5 (35.7)	3 (8.1)	2 (10.5)
Abnormal	2 (50.0)	6 (75.0)	1 (50.0)	9 (64.3)	30 (81.1)	15 (78.9)
Not examined	0	0	0	0	0	0
Primitive reflexes						
Normal	1 (25.0)	0	0	1 (7.1)	0	0
Abnormal	2 (50.0)	0	0	2 (14.3)	0	0
Not examined	0	1 (12.5)	0	2 (14.3)	0	0

Source: EMA D166 update (2022). Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=Full Analysis Set; GMAS=Genotype-Matched Analysis Set. † Six out of the eight patients who participated in study MCD-501 also participated in study MCD-201. Additionally, two patients, who had previously received rcPMP treatment through named-patient use but were not part of the MCD-501 study, were enrolled in MCD-201.(49)

Table 26: Summary of neurologic examination results at the last assessment (PFAS, data cut-off 31st October 2020)

Parameter result	cPMP-treated patients (N=10) n (%)	Untreated controls (N=14) n (%)
Spontaneous movement		
Normal	3 (30.0)	1 (7.1)
Abnormal	6 (60.0)	13 (92.9)
Not examined	1 (10.0)	0
Truncal tone		
Normal	3 (30.0)	1 (7.1)
Abnormal	7 (70.0)	13 (92.9)
Not examined	0	0
Appendicular tone		
Normal	1 (10.0)	0
Abnormal	8 (80.0)	14 (100)
Not examined	1 (10.0)	0
Deep tendon reflexes		
Normal	3 (30.0)	1 (7.1)
Abnormal	7 (70.0)	13 (92.9)
Not examined	0	0
Primitive reflexes		

Parameter result	cPMP-treated patients (N=10) n (%)	Untreated controls (N=14) n (%)
Normal	0	0
Abnormal	0	0
Not examined	2 (20.0)	0

Source: EMA D166 update (2022). Note: The six patients who were treated with rcPMP on study MCD-501 and went on to enrol in study MCD-201 are only presented in the MCD-201 column.

B.2.7 Subgroup analysis

The following section presents key efficacy results in subpopulations, including time of cPMP treatment initiation and gender. Because all 14 treated patients had MoCD symptom onset within 28 days of birth, no conclusions can be drawn regarding time of symptom onset.(34-37)

Treatment initiation

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

Overall survival

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

Feeding pattern, growth, and mobility

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

Data is available for GMFCS-ER and for the evaluation of unassisted sitting for 9/10 patients included in the prospective studies MCD-201 and MCD-202 (no developmental data was available for one patient from study MCD-202 due to the patient's discontinuation from the study on Day 13).

Patients who initiated treatment within 14 days of birth were more likely to be ambulatory (4/7, 57.1%) compared with those who initiated treatment later (0/2, 0%). Similarly, patients who initiated treatment within 14 days of birth were more likely to be able to sit unassisted (6/7, 85.7%) compared with those who initiated treatment later (0/2, 0%).

Seizures and Neurologic examination

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

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

Gender

Overall survival

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

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

Other efficacy parameters

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

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

Treated patients of both genders were more likely to be able to sit unassisted at any time compared with untreated controls. Among males, 3 of 4 treated patients (75.0%) compared with 3 of 21 untreated patients (14.3%) could sit unassisted at any time. Similarly, for females, 3 of 5 treated patients (60.0%) compared with none of the six untreated patients (0%) could sit unassisted.

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

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

B.2.8 Meta-analysis

No relevant meta-analyses were conducted for inclusion in this submission.

B.2.9 Indirect and mixed treatment comparisons

No relevant indirect or mixed treatment comparisons were conducted for inclusion in this submission.

B.2.10 Adverse reactions

B.2.10.1 Treatment exposure

In study MCD-501, 15 patients were enrolled with suspected MoCD Type A who were treated on a named-patient basis with rcPMP (80-240 µg/kg per day). 10 of these patients were confirmed to have MoCD Type A, 4 were diagnosed with MoCD Type B, and one had an unknown diagnosis. In study MCD-201, 8 patients were treated with fosdenopterin, all of whom had previously received rcPMP. In the

ongoing study MCD-202, 5 treatment-naïve patients have been treated with fosdenopterin thus far: 3 were confirmed to have MoCD Type A and two patients were diagnosed with MoCD Type B. The dose of cPMP was gradually increased over the course of the treatment for most patients, for the duration of treatment per quantity of the dose received for patients with MoCD Type A. Patients with MoCD Type B or an unknown diagnosis were treated between 3 and 17 days before treatment was discontinued.

Across the 15 treated patients, overall patient-years of exposure to cPMP – from the first dose of rcPMP to the last dose of fosdenopterin as of the MAA safety update data cut-off period (31st October 2021) – was substantial, at 83.0 patient-years.

Median total time on cPMP was 1,960 days (5.4 years) and ranged from 6 days to 4,896 days (13.4 years). As of the data cut-off for the safety update (31st October 2021), 10 patients were ongoing on treatment with fosdenopterin, including eight patients in study MCD-201 and two patients in study MCD-202.(49)

B.2.10.2 Summary of treatment-emergent adverse events

A summary of the overall incidence of treatment-emergent adverse events (TEAEs) is presented by study in Table 27. In study MCD-501, severity and causality were only collected for serious adverse events (SAEs). As of the data cut-off of the MAA safety update, 31 October 2021, all 11 patients in studies MCD-201 and MCD-202 experienced at least one TEAE. New TEAEs reported during the period were assessed as treatment-related for two additional patients, and one additional patient experienced severe TEAEs.(49)

Table 27: Overall summary of TEAEs (Safety Set: Patients with MoCD Type A, MAA safety update data cut-off 31 October 2021)

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

Patients with:	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Any TEAE leading to dose modification	0	0	0
Any TEAE leading to treatment discontinuation	0	0	0

Source: EMA D166 update (2022). Abbreviations: MoCD=molybdenum cofactor deficiency; NA=not available; SAE=serious adverse event; TEAE=treatment-emergent adverse event. [a] in study MCD-501, severity and causality were collected only for SAEs. Note: Six of the ten patients in study MCD-501 were also treated with fosdenopterin in study MCD-201. (49)

B.2.10.3 Frequency of treatment-emergent adverse events

The specific TEAEs, categorised by MedDRA system organ class and preferred term occurring in more than one patient when combining the studies MCD-501, MCD-201 and MCD-202, are shown in Table 28.

Table 28: TEAEs Reported in >1 Patient by MedDRA system organ class and PT (safety set: patients with MoCD Type A, MAA safety update data cut-off 31st October 2021)

System organ class preferred term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Patients with at least one adverse event	9 (90.0)	8 (100.0)	3 (100.0)
Infections and infestations	8 (80.0)	8 (100.0)	2 (66.7)
Pneumonia	3 (30.0)	3 (37.5)	1 (33.3)
Viral infection	0	5 (62.5)	1 (33.3)
Upper respiratory tract infection	3 (30.0)	2 (25.0)	0
Device-related infection	3 (30.0)	1 (12.5)	0
Influenza	0	4 (50.0)	0
Sepsis	2 (20.0)	2 (25.0)	0
Catheter site infection	0	2 (25.0)	1 (33.3)
Gastroenteritis	1 (10.0)	1 (12.5)	1 (33.3)
Gastroenteritis viral	0	2 (25.0)	1 (33.3)
Oral candidiasis	2 (20.0)	1 (12.5)	0
Varicella	2 (20.0)	1 (12.5)	0
Bacteraemia	0	1 (12.5)	1 (33.3)
Bronchitis	1 (10.0)	1 (12.5)	1 (33.3)
Device-related sepsis	2 (20.0)	0	0
Ear infection	0	2 (25.0)	0
Fungal skin infection	2 (20.0)	0	0
Lower respiratory tract infection	0	3 (37.5)	0

System organ class preferred term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Nasopharyngitis	0	2 (25.0)	1 (33.3)
Otitis media acute	0	1 (12.5)	1 (33.3)
Respiratory tract infection	1 (10.0)	1 (12.5)	0
Urinary tract infection	1 (10.0)	2 (25.0)	0
Vascular device infection	0	2 (25.0)	0
Viral tonsillitis	0	1 (12.5)	1 (33.3)
Viral upper respiratory tract infection	0	2 (25.0)	0
General disorders and administration site conditions	8 (80.0)	7 (87.5)	1 (33.3)
Pyrexia	3 (30.0)	6 (75.0)	1 (33.3)
Complications associated with device	0	6 (75.0)	1 (33.3)
Catheter site discharge	0	2 (25.0)	0
Catheter site extravasation	0	2 (25.0)	0
Catheter site haemorrhage	0	1 (12.5)	1 (33.3)
Catheter site inflammation	1 (10.0)	1 (12.5)	0
Catheter site pain	0	2 (25.0)	0
Device dislocation [a]	2 (20.0)	0	0
Device leakage [a]	2 (20.0)	0	0
Medical device complication	2 (20.0)	0	0
Respiratory, thoracic and mediastinal disorders	5 (50.0)	7 (87.5)	2 (66.7)
Cough	1 (10.0)	4 (50.0)	1 (33.3)
Sneezing	1 (10.0)	2 (25.0)	0
Asthma	1 (10.0)	1 (12.5)	0
Epistaxis	0	2 (25.0)	0
Oropharyngeal pain	0	2 (25.0)	0
Rhinorrhoea	1 (10.0)	0	1 (33.3)
Skin and subcutaneous tissue disorders	5 (50.0)	7 (87.5)	2 (66.7)
Rash	0	3 (37.5)	0
Dermatitis	1 (10.0)	0	1 (33.3)
Eczema	2 (20.0)	0	1 (33.3)
Rash maculo-papular	0	2 (25.0)	0
Skin disorder	0	2 (25.0)	0
Gastrointestinal disorders	4 (40.0)	6 (75.0)	2 (66.7)
Vomiting	0	3 (37.5)	2 (66.7)

System organ class preferred term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Diarrhoea	0	2 (25.0)	1 (33.3)
Abdominal pain	0	2 (25.0)	0
Constipation	1 (10.0)	1 (12.5)	0
Injury, poisoning and procedural complications	0	6 (75.0)	1 (33.3)
Contusion	0	1 (12.5)	1 (33.3)
Blood and lymphatic system disorders	2 (20.0)	3 (37.5)	1 (33.3)
Anaemia	2 (20.0)	1 (12.5)	1 (33.3)
Eye disorders	2 (20.0)	3 (37.5)	1 (33.3)
Conjunctival haemorrhage	1 (10.0)	0	1 (33.3)
Eye swelling	0	2 (25.0)	0
Strabismus	1 (10.0)	1 (12.5)	0
Nervous system disorders	1 (10.0)	4 (50.0)	1 (33.3)
Seizure	0	2 (25.0)	1 (33.3)
Metabolism and nutrition disorders	0	2 (25.0)	2 (66.7)
Hypoglycaemia	0	0	2 (66.7)
Product issues	0	4 (50.0)	0
Device dislocation [a]	0	3 (37.5)	0
Device leakage [a]	0	2 (25.0)	1 (33.3)
Device occlusion	0	2 (25.0)	0
Psychiatric disorders	1 (10.0)	3 (37.5)	0
Agitation	0	2 (25.0)	0
Irritability	1 (10.0)	1 (12.5)	0
Surgical and medical procedures	2 (20.0)	1 (12.5)	1 (33.3)
Central venous catheterisation	0	1 (12.5)	1 (33.3)

Source: EMA D166 update (2022). Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; MoCD=molybdenum cofactor deficiency; Note: six of the ten patients in study MCD-501 were also treated with fosdenopterin in study MCD-201. [a] Coding was conducted using MedDRA version 17.0 in study MCD-501 and MedDRA version 21.1 in studies MCD-201 and MCD-202; the system organ class for these PTs (device dislocation and device leakage) was modified between these two versions of the dictionary.(49)

Device-related complications

Among the 11 patients who received fosdenopterin in studies MCD-201 and MCD-202, 10 experienced at least one device-related TEAE. The events reported in more than one patient included complication associated with device, device dislocation and catheter site infection, catheter site extravasation, catheter site pain, central

venous catheterisation, catheter site discharge, device leakage, device occlusion, bacteraemia, sepsis, and vascular device infection. In all ten patients, device-related events were reported as serious, and all were considered unrelated to study treatment.

Most serious device-related complications were associated with infections, including preferred terms of catheter site abscess/infection, vascular device infection, sepsis, device-related infection, and bacteraemia, or were reported as complications with the device, including preferred terms of complication associated with device, device leakage, and device dislocation.

Skin disorders

Overall, skin and subcutaneous tissue disorders were reported in five patients in study MCD-501, 7 patients in study MCD-201, and two patients in study MCD-202. The events within the skin and subcutaneous tissue disorders system organ class reported in >1 patient overall were rash (3 patients) and dermatitis, eczema, maculopapular rash, and skin disorder (verbatim term: skin defect nearby port central venous line with risk of dislocation; two patients each). One event of skin disorder due to a skin defect near the port central venous line (study MCD-201) was assessed as serious and severe in intensity. No other events in this system organ class were severe in intensity or reported as serious.

Phototoxicity

One notable safety concern (i.e., a potential risk of phototoxicity) was identified in the nonclinical toxicology programme. In vitro and in vivo animal studies demonstrated phototoxic effects of fosdenopterin. During clinical studies up until the cut-off date of 31st October 2021 (MAA safety update), there have been two reports of skin-related AEs, redness with sun exposure, reported as mild and resolved. However, causality to fosdenopterin treatment cannot be established.

B.2.10.4 Serious adverse events/deaths

The majority of patients reported at least one SAE, including 8 of 10 patients during treatment with rcPMP (study MCD-501) and 9 of 11 patients during treatment with fosdenopterin (studies MCD-201 and MCD-202). All SAEs except for one report of necrotising enterocolitis (study MCD-501) were assessed by the Investigator as unrelated to treatment.

The most reported types of SAEs were device/catheter-related events and infections. Most SAEs were reported in only one patient. Serious AEs by MedDRA PT reported in more than one patient in study MCD-501 were device-related infection (3 patients) and pneumonia, sepsis, device-related sepsis, pyrexia, medical device complication, and device dislocation (2 patients each). In patients who received fosdenopterin, SAEs reported in more than one patient were complications associated with the device (5 patients), pneumonia (3 patients), and pyrexia, lower respiratory tract infection, vascular device infection, viral infection, bacteraemia, device leakage, device-related infection, and central venous catheterisation (2 patients each).

A total of three deaths were reported across the four clinical studies, including two patients with MoCD Type A (study MCD-501) who died while receiving rcPMP under named-patient-patient use from RSV pneumonia and necrotising enterocolitis, respectively, and one patient with MoCD Type B who died more than 2 years post-treatment of an unknown cause. The death due to necrotising enterocolitis was assessed as possibly related to treatment with rcPMP. This patient had a complicated medical course, receiving multiple concurrent treatments, and died at 6 days of age.(40)

There were no deaths among the 11 MoCD Type A patients who were treated with fosdenopterin in studies MCD-201 and MCD-202, with 10 of 11 patients still undergoing treatment as of the 31st October 2021 data cut-off for the MAA safety update, having received up to 8 years of treatment at that time.

There were no other treatment-related SAEs in studies MCD-201 and MCD-202, including no hypersensitivity or acute infusion-related reactions associated with the administration of cPMP in any patient.

Table 29: Treatment-emergent SAEs by MedDRA system organ class and PT (safety set: patients with MoCD Type A, MAA safety update data cut-off 31 October 2021)

System organ class preferred term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Patients with at least one SAE	8 (80.0)	7 (87.5)	2 (66.7)
Infections and infestations	6 (60.0)	6 (75.0)	1 (33.3)
Pneumonia	2 (20.0)	2 (25.0)	1 (33.3)
Device-related infection	3 (30.0)	1 (12.5)	0
Sepsis	2 (20.0)	1 (12.5)	0

System organ class preferred term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Bacteraemia	0	1 (12.5)	1 (33.3)
Catheter site infection	0	2 (25.0)	0
Device-related sepsis	2 (20.0)	0	0
Lower respiratory tract infection	0	2 (25.0)	0
Vascular device infection	0	2 (25.0)	0
Viral infection	0	1 (12.5)	1 (33.3)
Catheter site abscess	0	1 (12.5)	0
Febrile infection	1 (10.0)	0	0
Gastroenteritis	0	0	1 (33.3)
Gastroenteritis viral	0	0	1 (33.3)
Infection	1 (10.0)	0	0
Otitis media	0	1 (12.5)	0
Pneumonia influenza	0	1 (12.5)	0
Pneumonia RSV	1 (10.0)	0	0
Respiratory tract infection	1 (10.0)	0	0
Rhinovirus infection	0	1 (12.5)	0
Staphylococcal infection	1 (10.0)	0	0
Staphylococcal sepsis	1 (10.0)	0	0
Upper respiratory tract infection	1 (10.0)	0	0
Urinary tract infection	0	1 (12.5)	0
Varicella	1 (10.0)	0	0
Viral tonsillitis	0	0	1 (33.3)
Viral upper respiratory tract infection	0	1 (12.5)	0
General disorders and administration site conditions	5 (50.0)	5 (62.5)	1 (33.3)
Complication associated with device	0	4 (50.0)	1 (33.3)
Pyrexia	2 (20.0)	2 (25.0)	0
Device dislocation [a]	2 (20.0)	0	0
Medical device complication	2 (20.0)	0	0
Catheter site discharge	0	1 (12.5)	0
Catheter site extravasation	0	1 (12.5)	0
Catheter site inflammation	0	1 (12.5)	0
Catheter site swelling	0	0	1 (33.3)
Device leakage [a]	1 (10.0)	0	0
Swelling	0	1 (12.5)	0

System organ class preferred term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Respiratory, thoracic, and mediastinal disorders	2 (20.0)	1 (12.5)	1 (33.3)
Apnoea	0	0	1 (33.3)
Pleural effusion	1 (10.0)	0	0
Pneumonia aspiration	0	1 (12.5)	0
Respiratory distress	1 (10.0)	0	0
Respiratory failure	0	1 (12.5)	0
Upper airway obstruction	0	1 (12.5)	0
Gastrointestinal disorders	2 (20.0)	0	1 (33.3)
Erosive oesophagitis	0	1 (12.5)	0
Necrotising colitis	1 (10.0)	0	0
Stomatitis	1 (10.0)	0	0
Vomiting	0	0	1 (33.3)
Metabolism and nutrition disorders	0	2 (25.0)	0
Dehydration	0	1 (12.5)	0
Diabetic ketoacidosis	0	1 (12.5)	0
Type 1 diabetes mellitus	0	1 (12.5)	0
Product issues	0	1 (12.5)	0
Device dislocation [a]	0	1 (12.5)	0
Device leakage [a]	0	1 (12.5)	0
Nervous system disorders	1 (10.0)	1 (12.5)	1 (33.3)
Epilepsy	0	1 (12.5)	0
Myoclonus	1 (10.0)	0	0
Seizure	0	0	1 (33.3)
Subdural effusion	1 (10.0)	0	0
Surgical and medical procedures	0	1 (12.5)	1 (33.3)
Central venous catheterisation	0	1 (12.5)	1 (33.3)
Psychiatric disorders	1 (10.0)	0	0
Irritability	1 (10.0)	0	0
Skin and subcutaneous tissue disorders	0	1 (12.5)	0
Skin disorder	0	1 (12.5)	0
Vascular disorders	0	1 (12.5)	0
Venous thrombosis	0	1 (12.5)	0

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

B.2.11 Ongoing studies

Because fosdenopterin was granted marketing authorisation under exceptional circumstances, the company is required to conduct a noninterventional post-authorisation safety study (NI-PASS). The primary objective of the NI-PASS is the active collection of long-term safety data. The secondary objective is the collection of effectiveness data of all treated patients.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Summary of clinical efficacy

The outcomes assessed have significant relevance in addressing unmet need for patients with MoCD Type A. Overall, fosdenopterin offers the potential to improve survival, enhance feeding abilities, promote better motor function, facilitate cognitive development, and positively influence neurological examinations in patients with MoCD Type A. While individual patient responses may vary, the data indicates a clear and positive impact of fosdenopterin/rcPMP on various aspects of patient wellbeing and functional outcomes.(49) The following section expands on these clinical benefits.

Overall survival

Fosdenopterin/rcPMP has been shown to significantly improve OS in patients. Compared to the natural history cohort where a significant number of patients had died, the treated population had a higher proportion of patients who were alive and receiving treatment at the data cut-off, indicating that fosdenopterin can extend the life of patients with MoCD Type A.(49)

Feeding status

Untreated patients often require feeding tubes for nutrition.(7) However, in the treated cohort, the median time to sustained non-oral feeding was significantly delayed, demonstrating that fosdenopterin allows patients to maintain their ability to feed orally for a longer period of time and thus reduces the need for non-oral feeding interventions.(49) This outcome can improve the daily lives of patients and reduce the burden on caregivers.

Developmental assessments

Improved motor function

Fosdenopterin/rcPMP has shown positive effects on gross motor function, with treated patients (particularly those the early-onset form of the disease) exhibiting better motor function compared to natural history controls. A larger proportion of treated patients were able to achieve ambulatory status without restriction, indicating improved mobility and motor capabilities.(49) By improving mobility and independence, patients can participate more actively in normal activities.

Improved cognitive development

Fosdenopterin demonstrated potential improvements in Cognitive, Fine Motor and Gross Motor domains of the Bayley test, in contrast to the low functioning recorded in the natural history control group. Fosdenopterin/rcPMP may offer improved cognitive development beyond what would be expected based on the natural disease progression.(49) This will hopefully enhance patients' learning abilities, communication skills and overall cognitive functioning, leading to a better quality of life and increased independence.

Improved neurological examinations

Despite the prevalence of baseline neurological damage, treated patients showed improvements in various neurological parameters, suggesting a positive impact on the overall neurological status of patients with MoCD Type A.(49) Improved neurological status may reduce the need for interventions to mitigate neurological symptoms. This will hopefully improve any neurological deficits and reduce the need for interventions to mitigate neurological symptoms.

B.2.12.2 Summary of clinical safety

Fosdenopterin/rcPMP demonstrates a manageable safety profile, with the most frequently reported adverse events related to central line complications or respiratory tract and viral infections which are also commonly observed in healthy children. As fosdenopterin is structurally identical to rcPMP, the expected safety profile aligns with observations from clinical studies, although potential phototoxicity cannot be conclusively ruled out.(23)

B.2.12.3 Strengths and limitations of the clinical evidence base

The interventional studies were carefully designed, considering the rarity and severity of MoCD Type A. They collected data on key outcomes in a transparent and prospective manner, and the consistency of design and outcomes across all three investigations ensured that all outcomes relevant to MoCD Type A were captured. (49)

The evidence consistently shows that fosdenopterin/rcPMP provides immediate, significant, and long-term improvements across all outcomes, including survival, biomarkers, feeding patterns, growth metrics, and developmental assessments. This is strengthened by a genotype-matched and weighted comparative analyses to natural history cohort.(49)

The median total time on fosdenopterin/rcPMP was 5.4 years, and this follow-up provides a considerable amount of data on long-term outcomes, which is especially noteworthy given MoCD Type A's rarity.(49)

While the evidence of fosdenopterin/rcPMP’s therapeutic and safety efficacy is clear, inherent limitations exist due to the rare and extremely debilitating nature of the condition.(49)

The data contains only 15 treated cases, demonstrating the ultra-rare nature of the illness; nevertheless, one patient from England was included. The company does not anticipate any problems with the trials' generalisability to the English population.(49)

The studies are open-label, non-RCT, and single-arm, which is necessary given the lack of licensed treatments for the ultra-rare and severe nature of MoCD Type A. Ethical considerations make including a control arm difficult; however, the natural history study MCD-502 serves as an ideal comparison group from which to derive findings on comparative effectiveness.(49)

B.2.12.4 Conclusion

In summary, the available data strongly supports the benefits of fosdenopterin for patients with MoCD Type A. The treatment shows significant improvements in overall survival, feeding abilities, motor function, cognitive development, and neurological examinations. Despite study limitations due to the rare nature of the condition, the

evidence consistently demonstrates the positive impact of fosdenopterin across various critical aspects.(49)

The survival benefit of fosdenopterin is evident, with a higher proportion of treated patients alive compared to the natural history cohort. This extended lifespan, coupled with positive clinical outcomes, highlights the potential of fosdenopterin in improving the quality of life of patients and their caregivers.(49)

The delayed transition to sustained non-oral feeding also indicates a practical benefit, reducing the burden on patients and caregivers. Additionally, fosdenopterin’s positive effects on motor function, cognitive development, and neurological status entail promising improvements in patients' mobility, independence, and cognitive functioning.(49)

Despite the studies’ limitations, most notably a small sample size due to the ultra-rare nature of MoCD Type A, the evidence consistently supports fosdenopterin's immediate and long-term therapeutic benefits. Overall, fosdenopterin stands as a crucial intervention for MoCD Type A.(49)

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

No published cost-effectiveness analyses were identified as part of the SLR. A proxy SLR was performed in Dravet syndrome, which reported 23 published cost-effectiveness analyses; these are outlined in Appendix G.

B.3.2 Economic analysis

The following chapter reports the economic evaluation in support of the submission for fosdenopterin in the treatment of MoCD Type A. The objective of the economic evaluation is to assess the cost-effectiveness of fosdenopterin compared to standard of care (SoC) for the treatment of MoCD Type A, from the perspective of the NHS in England and Wales. As described in the clinical section, MoCD Type A is a fatal disorder with no existing treatments and high mortality. Due to the rarity of the condition, limited data exist. Every attempt has been made to adequately characterise and evaluate the cost-effectiveness of fosdenopterin in MoCD Type A by using the best available proxy data and eliciting clinical expert opinion.

B.3.2.1 Patient population

The modelled patient population for health economic evaluation is all patients with MoCD Type A in England and Wales. This is aligned with the licensed indication of fosdenopterin within the EU.(33)

The marketing authorisation includes patients with suspected MoCD Type A (i.e. presumptive diagnosis), after which a genetic test is performed to confirm diagnosis. Treatment with fosdenopterin is either maintained or discontinued based on test results. [redacted]

B.3.2.2 Model perspective

In line with NICE guidelines, the NHS and Personal and Social Services (PSS) perspective was used for the base-case analysis. Only direct healthcare costs incurred by the NHS such as drug costs, adverse event costs and disease management costs are included in the base-case. Given the severity of MoCD Type A, it was considered appropriate to include the quality of life for caregivers in the

model base-case. This is in line with the NICE Reference Case, given MoCD Type A is expected to directly impact caregivers as well as patients.

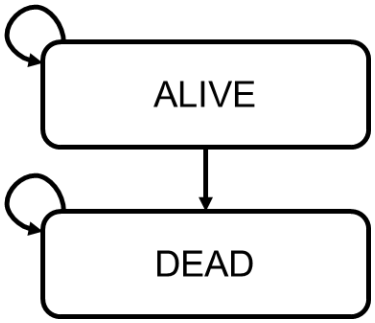
B.3.2.3 Model structure

A two-state survival model was developed in Microsoft Excel to evaluate the cost-effectiveness of fosdenopterin versus SoC (see Figure 11). The primary indicated benefit of treatment with fosdenopterin is improved patient survival. As such, a two-state survival model with health states describing patients who are 'alive' or 'dead' is used capture the incremental benefit of treatment on patient survival, with death an absorbing health state. MoCD Type A is also characterised by the incidence of seizures, difficulty feeding, and compromised mobility.(26) Early treatment with fosdenopterin is primarily anticipated to impact survival, but also to limit the progression of these symptoms (i.e. a stabilisation in the incidence of seizures, meaning that seizures do not increase in frequency or severity once treatment starts a reduced need for nasogastric feeding and no worsening in mobility).(49) The model therefore considers the impact of improvement on survival and patient quality of life. Due to the paucity of data describing the natural history of MoCD type A, these additional benefits have not been captured as distinct health states within the model. However, these are captured indirectly as part of the base-case in the calculation of incremental costs and quality of life analysis for patients treated with fosdenopterin in comparison with SoC.

All patients enter the model in the 'alive' state, and either remain alive or have a per-cycle risk of transition to the 'dead' health state. For those treated with fosdenopterin the reduction in the risk of death was informed by data from the supporting global clinical trial programme.(34-37) The probability of patient death in the control arm is estimated based on survival data collected in studies MCD-201, MCD-202, MCD-501 and MCD-502, with patients who do not die in that model cycle remaining in the 'alive' state. The long-term survival of those in the alive state was extrapolated using parametric survival analysis, in line with Technical Support Document 14 (54), to estimate patient life expectancy over a lifetime horizon of 100 years, with the impact of uncertainty in long-term outcomes assessed through sensitivity analysis.

Utilities and costs are attached to each health state, with values conditional on the treatment a patient is receiving. As such, patient health state membership over each model cycle informs the accrual of direct costs and health benefits.

Figure 11. Model schematic



B.3.2.4 Features of the economic analysis

A summary of the key features of the economic model is provided in Table 30.

Table 30: Key features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime (maximum age of 100) Life tables from the Office for National Statistics are applied in the model to ensure long-term survival reflects increased risk of death as patients age, with disease-specific mortality based on extrapolation of clinical trial data.(55)	Fosdenopterin is expected to be administered for a lifetime, and the benefits of treatment are expected to be applicable to a lifetime horizon. This is in line with the NICE Reference Case.
Model cycle length	Four weeks	This cycle length was chosen as the symptoms of MoCD Type A can progress rapidly following birth, and similarly, the benefit of treatment with fosdenopterin in ameliorating further symptoms and risk of mortality is anticipated to occur rapidly due to the method of action. As such, four weeks is sufficiently short to capture underlying disease and symptom progression associated with MoCD Type A, in addition to the incremental costs and benefits of treatment with fosdenopterin over the model time horizon.

	Current evaluation	
Discounting	Costs and quality-adjusted life-years (QALYs) are discounted using a 3.5% discount rate.	In line with NICE Reference Case.
Source of utilities	QoL data was not collected in the study programme for fosdenopterin. The QoL SLR did not reveal any direct sources for utilities in MoCD Type A for use in the model. Therefore, a proxy from Dravet syndrome was applied in the model using EQ-5D values. (56)	No direct estimates were available, and results from the proxy SLR were therefore used. The selected source is recent (2018) and collected EQ-5D in many patients (N=584). The selection of EQ-5D is in line with the NICE Reference Case.
Source of costs	Perspective of the NHS and PSS in England and Wales.	All costs relate NHS and PSS resources and are valued using the prices relevant to the NHS and PSS only.

Abbreviations: HST=highly specialised technology; MoCD=molybdenum cofactor deficiency; NHS=National Health Service; NICE=The National Institute for Health and Care Excellence; PSS=Personal and Social Services; QoL=quality of life; QALY=quality-adjusted life year.

B.3.2.5 Intervention technology and comparators

Substrate replacement therapy with fosdenopterin 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.

In line with NICE guidance, the choice of comparator in the model is guided by current clinical practice. There is no direct available comparator to fosdenopterin for the treatment of MoCD Type A, meaning the comparator is SoC. SoC for MoCD Type A consists of anticonvulsants to control seizures and nasogastric feeding.(7)

A scenario explores the inclusion of a low protein diet. Patients treated with fosdenopterin may still require supportive care with anticonvulsants. Therefore, this health economic evaluation is based on a comparison of fosdenopterin in addition to SoC versus SoC alone.

B.3.3 Clinical parameters and variables

The clinical data used in the economic evaluation include:

- Patient and general population characteristics
- Patient survival

- Treatment discontinuation and waning

Due to the rarity and severity of MoCD Type A and the paucity of data surrounding it, it is likely that the economic evaluation captures only those clinical inputs which can be quantified and sourced from the literature, and that a number of outcomes other than survival are not captured. These outcomes are more thoroughly described in Section B.3.11.

B.3.3.1 Patient population and characteristics

The health economic model is parameterised based on the patient population included in the fosdenopterin global clinical trial programme (Table 31). Patients enrolled in the prospective studies MCD-201 and MCD-202, as well as the retrospective, observational study MCD-501, informed outcomes in patients treated with fosdenopterin. Fosdenopterin and rcPMP were both used in the clinical studies. Because rcPMP and fosdenopterin are chemically equivalent, efficacy and safety data from rcPMP can be used to determine the safety and efficacy of fosdenopterin. As such, outcomes in patients treated with rcPMP in MCD-501 are assumed to be representative of patients treated with fosdenopterin, consistent with the analysis of the overall clinical trial programme. Patient data was pooled according to the treatment received for treatment-specific survival and pooled across all studies for estimation of population-level survival. A scenario analysis is presented using the early-onset population of MCD-502 (described as 'early-onset population', N=33) instead of the FAS (N=37). The data cut for all analyses included patient outcomes up to July 2019, reflecting the most recent available cut of individual patient-level data for analysis.

Table 31: Trial characteristics of studies used in the economic analysis

Study	Study type	Treatment regimen	Patient population	Population size (N)	Model arm
MCD-201	Prospective	Fosdenopterin	Paediatric MoCD Type A previously treated with rcPMP	7	Fosdenopterin
MCD-202	Prospective	Fosdenopterin	Treatment-naïve paediatric MoCD Type A	1	
MCD-501	Retrospective, observational	rcPMP	Paediatric MoCD Type A	4	
MCD-502 (FAS)	Natural history study (retrospective	None	Paediatric MoCD	37	SoC

	and prospective)				

Abbreviations: FAS, full analysis set; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant Escherichia coli-derived cyclic pyranopterin monophosphate.

The model requires demographic information for the modelled patient population, including age, sex, and weight percentile. Age and sex are used to inform the life table component of patient survival, as well as general population utility estimates used as baseline for calculation of health state utility decrements. The baseline age is zero in the model, as patients are expected to be diagnosed and receive treatment with fosdenopterin soon after birth.(33) The proportion of female patients is 30.6%, informed by the patient-level data from a pooled analysis of MCD-201, MCD-202, MCD-501 and MCD-502. Because patients with MoCD Type A typically exhibit reduced growth and failure to thrive, the model assumes patients follow the [redacted] percentile for total body weight in a UK general population, whereby all patients are assigned a weight corresponding to age 0 in the first cycle, up to a weight corresponding to age 100 in the final cycle. Weights were sourced from WHO growth charts until Month 60, and a 10% reduction to NHS Digital data weights was applied to construct an estimated [redacted] percentile weight band thereafter (in the absence of adult weight band data).(57) Given that the dosage of fosdenopterin is based on weight, this approach impacts the dose required for treatment, and consequently the cost of treatment.

B.3.3.2 Survival

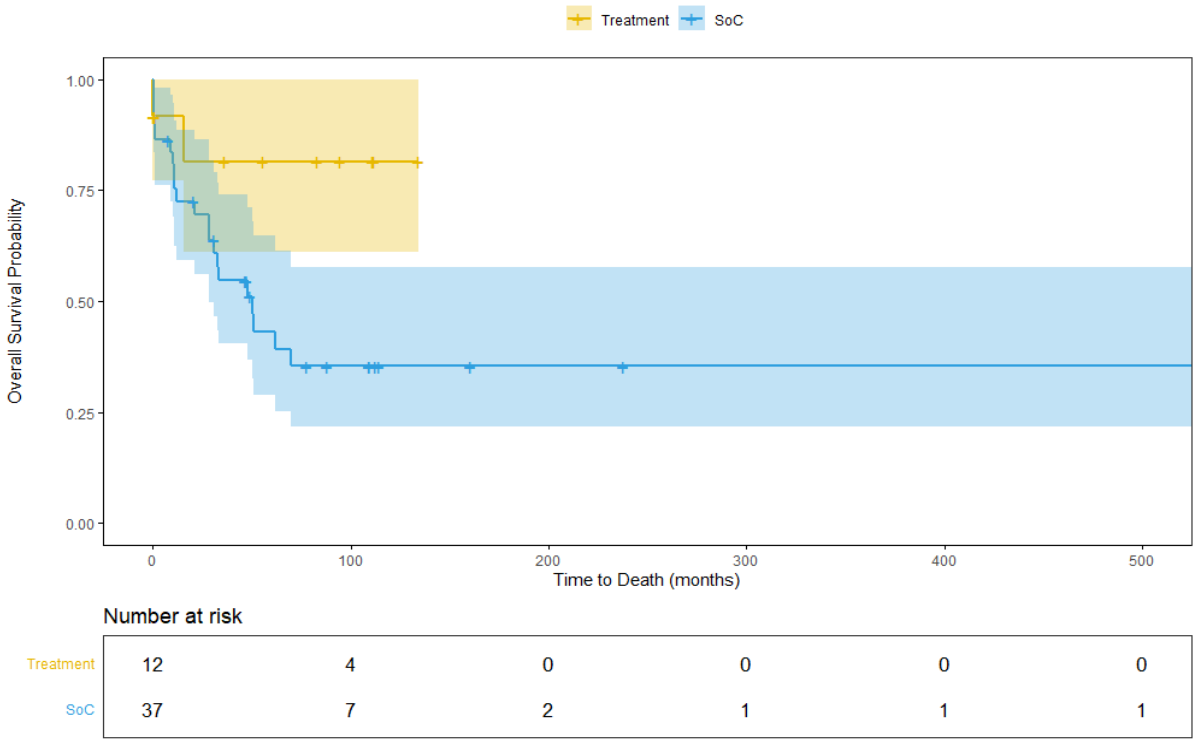
Survival analyses were conducted to quantify the improvement in survival associated with fosdenopterin, using patient-level data from studies MCD-201, MCD-202, MCD-501, and MCD-502 (see Table 31). The SoC arm was constructed using data from MCD-502 and consisted of 37 patients (FAS), contributing 2,309 person-months of follow-up. Survival outcomes for patients treated with fosdenopterin was based on data from MCD-201, MCD-202, and MCD-501 and included 12 patients, contributing a total of 757 person-months of follow-up. Kaplan-Meier plots of survival in both arms are presented in Figure 12.

Median survival for SoC was 50.7 months (95% CI: 28.8, NE) but was not estimable for the treatment arm given incomplete survival data. Notably, some patients in the SoC arm with milder phenotypes of MoCD Type A were observed to survive more than ten years from baseline, up to a maximum of 45 years. These observations,

combined with comparatively low patient numbers due to the ultra-rare nature of MoCD Type A, resulted in a significant plateau in patient survival from Month 70 onwards.

While survival estimates for both patients treated with fosdenopterin and SoC are incomplete, the majority of death events in the SoC arm were observed within follow-up, reducing the uncertainty associated with extrapolation of results over a lifetime horizon. Additionally, due to the method of action of fosdenopterin, the observed treatment effect is expected to be durable over a lifetime horizon. No waning effect is therefore included in the model.

Figure 12: Kaplan-Meier plot of overall survival for patients treated with fosdenopterin/rcPMP and untreated controls (SoC)



Abbreviations: rcPMP=recombinant Escherichia coli-derived cyclic pyranopterin monophosphate; SoC=standard of care.

To estimate long-term survival probabilities, parametric models were fit to the survival data for both the SoC and fosdenopterin arms. Here, a range of parametric distributions were considered in accordance with NICE TSD14 guidance, including Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma.(58) Survival models were fitted to the pooled all-patient population from the clinical trial programme, including a model parameter for the treatment group, with the coefficient

representing the treatment effect of fosdenopterin on survival. This approach assumes that hazards of mortality between treatment arms are proportional. Although this assumption is supported by observed data from the clinical trial, given that treatment with fosdenopterin is anticipated to halt disease progression, the assumption of proportional hazards between treatment arms may not be valid over a lifetime horizon. Model parameters for each parametric survival model are presented in Table 32, Table 33 and Table 34, with model extrapolations presented graphically in Figure 12.

Model fit was assessed both statistically, using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), and visually, to ensure the tails of the models aligned with clinical expectations of survival in patients with MoCD Type A.

Independent models were fit to extrapolate the Kaplan-Meier data in the base-case. Based on the clinical outcomes of MoCD Type A (mortality is extremely high) and visual inspection of the curves, the exponential distribution was considered the most plausible scenario for the SoC arm. The log-logistic distribution was selected in the fosdenopterin arm based on statistical fit. Clinical opinion (Appendix M) suggested that the range of extrapolations proposed was reflective of long-term prognoses; that is, patients who are treated early can expect a significant survival benefit in comparison with patients who receive no treatment with fosdenopterin. The Gompertz extrapolation was not considered plausible, as the underlying assumptions are not reflective of reality (i.e., a plateau in survival from approximately 100 months is not expected in treated patients (see Figure 13). As a result, the log-logistic distribution was selected: the corresponding curve lies midway through the range of distributions and present the lowest AIC/BIC scores (although differences with other model fits are less than five). Scenario analyses were conducted to test the robustness of cost-effectiveness conclusions to the choice of parametric distribution.

Table 32. Parameter coefficients, joint parametric models

Distribution	Parameter	Coefficient
Exponential	Treatment effect	-1.236
	Rate	0.009
Weibull	Treatment effect	2.509
	Shape	0.505
	Scale	132.237
Gompertz	Treatment effect	-1.311
	Shape	-0.027

	Rate	0.027
Log-logistic	Treatment effect	2.364
	Shape	0.631
	Scale	60.429
Log-normal	Treatment effect	1.932
	Mean	4.209
	SD	2.898
Gamma	Treatment effect	-2.507
	Shape	0.430
	Rate	0.002
Generalised gamma	Treatment effect	2.351
	μ	0.273
	σ	3.524
	Q	0.686

Abbreviations: AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; SD=standard deviation.

Table 33. Parameter coefficients, independent parametric models (fosdenopterin)

Distribution	Parameter	Coefficient
Exponential	Rate	0.003
Weibull	Shape	0.290
	Scale	17513.630
Gompertz	Shape	-0.117
	Rate	0.026
Log-logistic	Shape	0.309
	Scale	8410.481
Log-normal	Mean	9.683
	SD	6.102
Gamma	Shape	0.273
	Rate	0.000
Generalised gamma	μ	0.097
	σ	0.003
	Q	0.439

Abbreviations: AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; SD=standard deviation.

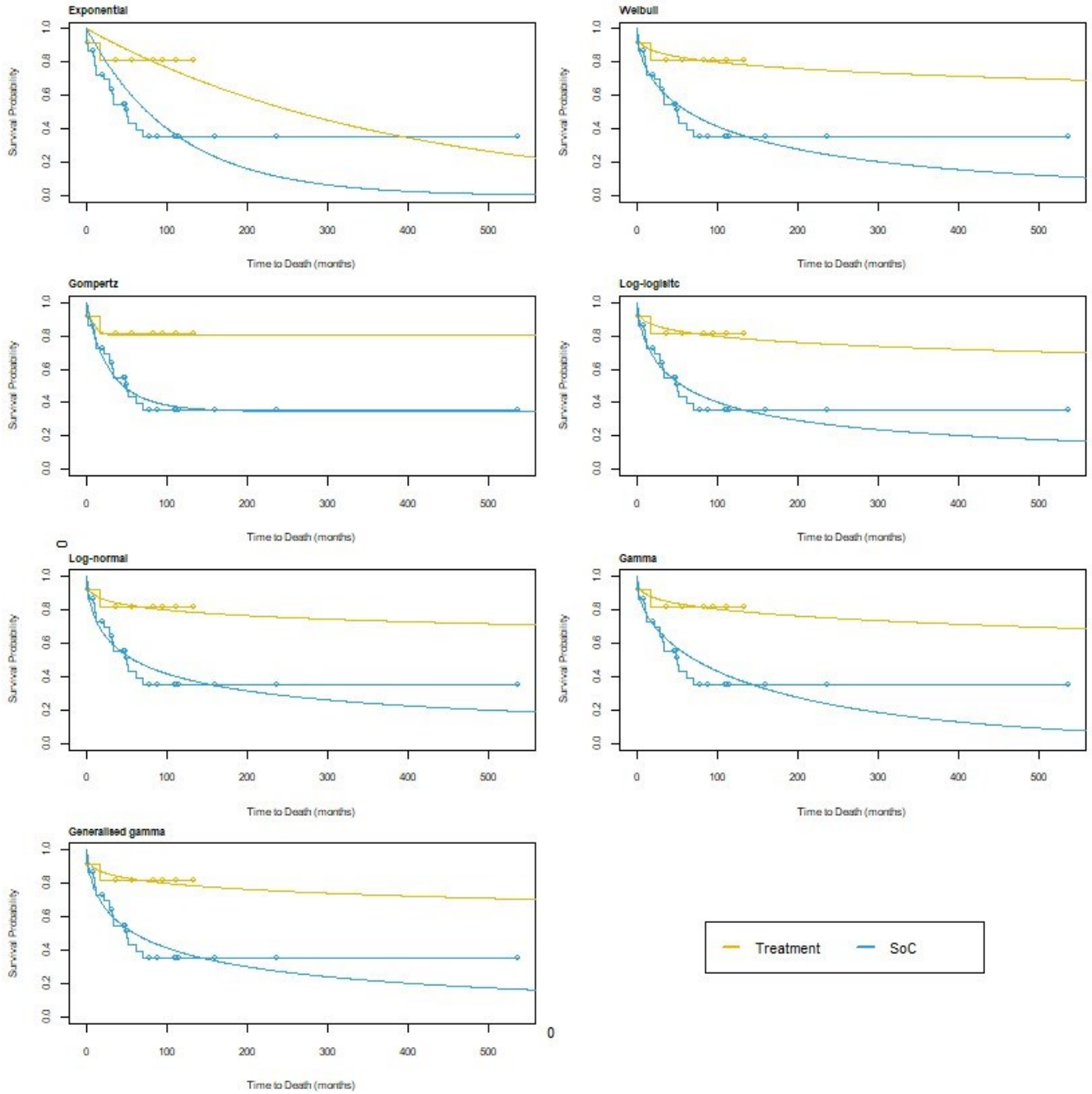
Table 34. Parameter coefficients, independent parametric models (SoC)

Distribution	Parameter	Coefficient
Exponential	Rate	0.009
Weibull	Shape	0.538
	Scale	126.942
Gompertz	Shape	-0.023
	Rate	0.025
Log-logistic	Shape	0.698
	Scale	56.926
Log-normal	Mean	4.064
	SD	2.536
Gamma	Shape	0.461

	Rate	0.003
Generalised gamma	μ	0.127
	σ	0.000
	Q	1.425

Abbreviations: AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; SD=standard deviation, SoC=Standard of Care.

Figure 13: Predicted long-term survival based on joint parametric models for patients treated with fosdenopterin/rcPMP and untreated controls (SoC)

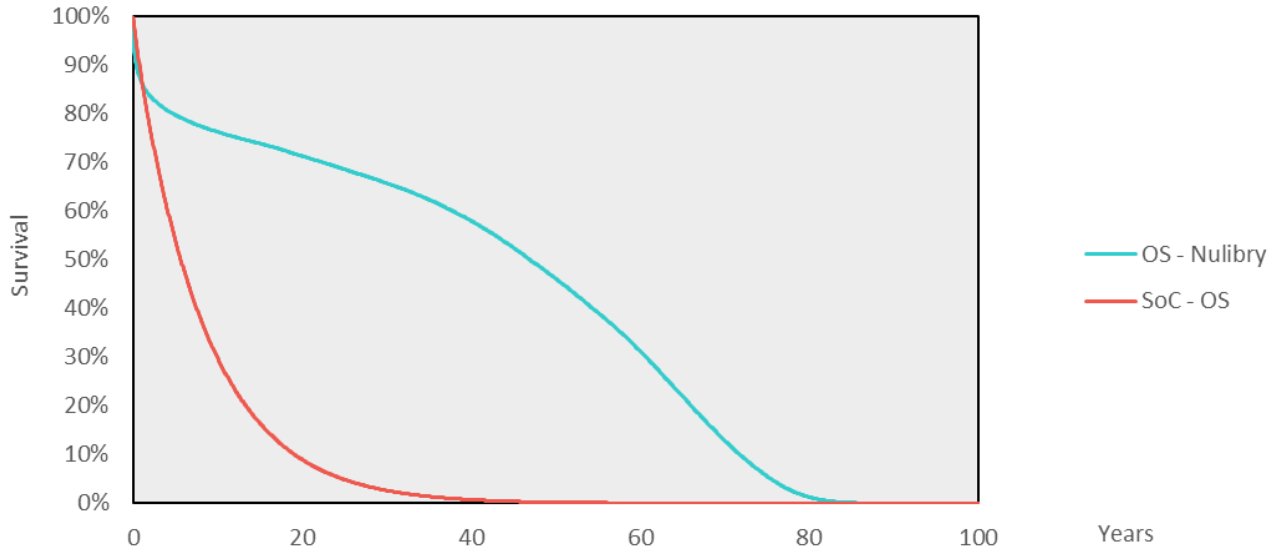


Please note: the Gompertz model in the fosdenopterin arm predicts a mortality rate of zero (i.e. a survival plateau) in the extrapolation of patient-level data and therefore does not appear on the panel.
Abbreviations: rcPMP=recombinant Escherichia coli-derived cyclic pyranopterin monophosphate; SoC=standard of care.

B.3.3.3 Life tables

Survival data collected in the trials was predominantly collected in paediatric patients. Therefore, to avoid underestimation of patient mortality in the model extrapolation, patient survival in the trials was assumed to be due to disease-specific causes, i.e., any deaths observed were attributed solely to MoCD Type A. Parametric survival predictions were combined with UK lifetables to reflect the increased all-cause risk of death over time. Because the prevalence of MoCD Type A is extremely low, any double counting of mortality risk resulting from this approach is negligible and can be disregarded. The base-case extrapolations are presented in Figure 14.

Figure 14: Survival extrapolations with general population mortality



Abbreviations: OS= overall survival; SoC= standard of care.

B.3.3.4 Discontinuation and waning

For the economic analyses, treatment discontinuation was not considered in the model as clinical consultation suggested patients were not anticipated to discontinue treatment due to the severity of MoCD Type A, except where a patient's prognosis of survival was extremely poor. The clinical study trial reported only one patient (3%) discontinuing treatment, with the reason for this being death; no patient or patient representative withdrew for any other reason. Similarly, because the method of action of fosdenopterin constitutes the replacement of the component needed to produce MoCo, efficacy waning is not expected and, thus, not included in the

economic model. Discontinuation is tested in scenario analysis at an annual rate of 1%.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

Quality of life was not collected as part of the clinical trial programme.

B.3.4.2 Mapping

No mapping was performed in the economic model.

B.3.4.3 Health-related quality of life studies

No health state utilities were identified as part of the quality of life SLR for MoCD Type A (see Appendix H). A proxy SLR was performed in Dravet syndrome, which identified 15 published articles reporting the quality of life in patients and/or caregivers. A large pan-European study for Dravet syndrome in 584 patients reporting EQ-5D-5L was selected in the base-case of the model.(56)

B.3.4.4 Adverse reactions

Utility decrements are modelled to capture the additional QoL impact of events beyond those captured in age-based utilities. Adverse event utility decrements are applied to all patients in a scenario (Table 35) in varying proportions. All adverse event utility decrements were taken from Sullivan et al. (59), and were assumed to reflect an annual loss in utility. All adverse events were included in the model, informed by the number of patients experiencing adverse events in the treatment arm (N=12). No adverse event data was available for the SoC arm. As such, the proportions were assumed equivalent in both arms, aside from events relating specifically to the administration of fosdenopterin (i.e. injury, poisoning, procedural complications and product issues; see Table 47), which were assumed not to occur in the SoC arm. The total utility decrement associated with adverse event incidence was adjusted for cycle length and was applied to patients in every cycle (Table 35).

Table 35. Adverse event utility decrements

Adverse event	Utility decrement	Description
General disorders and administration site condition	-0.0024	Other inflammatory condition of the skin
Infections and infestations	-0.0024	Other inflammatory condition of the skin

Gastrointestinal disorders	-0.0512	Gastrointestinal disorders
Skin and subcutaneous tissue disorders	-0.0006	Other skin disorders
Respiratory, thoracic and mediastinal disorders	-0.0336	Asthma
Injury, poisoning, procedural complications	-0.0512	Gastrointestinal disorders
Product issues	-0.0024	Other inflammatory condition of the skin
Eye disorders	-0.0092	Other eye disorders
Metabolism and nutrition disorders	-0.0839	Nutritional disorders
Nervous system disorders	-0.0695	Other nervous system disorder
Psychiatric disorders	-0.1009	Other mental conditions
Surgical and medical procedures	-0.0024	1Other inflammatory condition of the skin
Vascular disorders	-0.0531	Other circulatory disease
Cardiac disorders	-0.0246	Cardiac dysrhythmias
Ear and labyrinth disorders	-0.0103	Other ear and sense organ disorders
Musculoskeletal and connective tissue disorders	-0.0630	Other connective tissue disease
Hepatobiliary disorders	-0.0581	Hepatitis
Congenital, familial and genetic disorders	-0.0048	Other congenital anomalies
Immune system disorders	-0.0559	HIV infections
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-0.0086	Malignant neoplasm without specification

Abbreviations: AE=adverse event; ICD=international classification of diseases; SoC=standard of care.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

Because quality of life was not collected in the study programme for fosdenopterin, and the QoL SLR did not reveal any direct sources for utilities in MoCD Type A for use in the model, a proxy from the proxy SLR in Dravet syndrome was applied in the model (see Appendix H). The source from Lagae *et al.* was selected, as it collected EQ-5D for a range of ages (from birth to adulthood), was a large study including many patients (N=584), and is relatively recent (2018).(56) Although Dravet syndrome and MoCD Type A are different conditions with varying degrees of severity, it was considered the closest proxy to infer quality of life in the earlier years of life. This was discussed and confirmed with a clinical expert ([redacted], Medical Consultant to Sentynl Therapeutics, Appendix M).

Consultation with a clinical expert ([redacted], Medical Consultant to Sentynl Therapeutics) suggested that early treatment with fosdenopterin would result in long-term utilities comparable to the general population (see Appendix M). In the absence of clear estimates in patients with MoCD Type A, utilities in the

fosdenopterin arm are assumed equivalent to general population EQ-5D from Year 1 onwards. The sensitivity of model results to this assumption is assessed in scenario analysis, assuming more conservative utility estimates equivalent to a 50% improvement between SoC estimates and general population utilities. In the SoC arm, the Dravet proxy is applied from age 0 to 18, and a decline proportional to that of the general population is applied beyond 18 (Table 36). A summary of the utilities applied in the model is provided in Table 37.

Table 36. Utility values used in the model (56)

Age	Reported EQ-5D-5L
Infants (<2 years)	0.33
Preschool (2-5 years)	0.46
Middle childhood (6-11 years)	0.43
Adolescent (12-17 years)	0.43
Adult (18+ years)	0.34

Abbreviations: PedsQL=Paediatric Quality of Life Inventory; SoC=standard of care.

Table 37: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Alive	Age-based, variable. Based on Dravet syndrome and general population norms.	NA	B.3.4.2	Because no QoL evidence was identified for MoCD Type A, a proxy was used.
Dead	0	NA	B.3.4.5	Assumption.
General disorders and administration site condition	-0.0024	-0.0072415; 0.0025396	Table 35	Adverse event disutilities were sourced from the clinical trial (frequency) and a study in the UK (Sullivan et al).(59) All adverse events from the trial are included and those relating to the administration of fosdenopterin were excluded from the SoC arm.
Infections and infestations				
Gastrointestinal disorders	-0.0512	-0.0616124; -0.0407931		
Skin and subcutaneous tissue disorders	-0.0006	-0.002109; 0.0009515		
Respiratory, thoracic and mediastinal disorders	-0.0336	-0.0450645; -0.022049		
Injury, poisoning, procedural complications	-0.0512	0.0616124; -0.0407931		

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Product issues	-0.0024	-0.0072415; 0.0025396		
Eye disorders	-0.0092	-0.0201675; 0.0018529		
Metabolism and nutrition disorders	-0.0839	-0.1186075; -0.0491302		
Nervous system disorders	-0.0695	-0.0804682; -0.0584938		
Psychiatric disorders	-0.1009	-0.1102029; -0.0915732		
Surgical and medical procedures	-0.0024	-0.0072415; 0.0025396		
Vascular disorders	-0.0531	-0.0685985; -0.0376046		
Cardiac disorders	-0.0246	-0.0350775; -0.0141882		
Ear and labyrinth disorders	-0.0103	-0.0239164; 0.0034138		
Musculoskeletal and connective tissue disorders	-0.0630	-0.0714447; -0.0545134		
Hepatobiliary disorders	-0.0581	-0.0943754; -0.0217748		
Congenital, familial and genetic disorders	-0.0048	-0.0461836; 0.0365379		
Immune system disorders	-0.0559	-0.1124828; 0.0007617		
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	-0.0086	-0.0340315; 0.0169127		

Abbreviations: MoCD = molybdenum cofactor deficiency; SoC = Standard of Care.

Caregiver burden is included in the model base-case for patients in both arms. A caregiver disutility of -0.14 is used, in line with a submission in multiple sclerosis (TA254), reflecting the most severe health state (Expanded Disability Status Scale (EDSS) score 9) corresponding to 14.8 hours of care per day. This was considered consistent with the caregiving requirements for patients with MoCD Type A, given

the severity of their condition. A scenario analysis is included with a smaller disutility, reflective of an EDSS score of 7, corresponding to 5.6 hours of care daily (disutility of -0.05). The number of caregivers in the SoC arm is 1.8 (in line with TA808) and 1.0 in the treatment arm (reflective of the reduced need for caregiving when patients are adequately treated). Caregiving is applied until age 5 in the fosdenopterin arm. This is because once treatment is initiated, it is assumed there is no additional burden for caregivers. However, caregiver burden is applied for a lifetime in the SoC arm, as the severity of MoCD Type A is not expected to wane or diminish over time. A bereavement disutility of -0.04 is also included, following the methodology described in HST22 (60) whereby the disutility is applied to the proportion of patients who have died for the remaining life expectancy of the caregiver. This was considered appropriate given the severity of MoCD Type A and the significant toll on parents when losing a child, regardless of their age.

Caregiver utilities are modelled cumulatively to patient utilities and included in the calculation of total and incremental QALYs. The disutilities are applied to caregivers from age 32.3, which is the average age for parents in the UK, using general population EQ-5D from Ara and Brazier. (61, 62)

Table 38: Summary of parameters used in caregiver disutilities

Parameter	Fosdenopterin arm	SoC arm
Proportion of patients	100%	100%
Number of caregivers per patient	1	1.8
Patient age cap	5	100
Disutility for caregivers	-0.14	
Bereavement disutility	-0.04	
Age of caregiver at birth	32.3	

Abbreviations: SoC = standard of care.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

No published evidence was identified reporting costs and healthcare resource use estimates in MoCD Type A for use in the model (see Appendix I). A proxy SLR was performed in Dravet syndrome to support in finding relevant estimates. A total of 22 economic evaluations were identified reporting cost-effectiveness or costs associated with Dravet syndrome. For the purposes of the model, it was preferred to

use estimates from a previous NICE appraisal in Dravet syndrome (TA614) and input from [redacted], a Clinical Expert and Medical Consultant to Sentynl Therapeutics (see Appendix M).

B.3.5.1 Intervention and comparators' costs and resource use

Costs were calculated from the NHS and PSS perspective. The costing analysis incorporates up-to-date UK sources. Where needed, costs are inflated to 2023 using the Consumer Price Index (CPI).(63) The cost components consist of:

- Fosdenopterin acquisition
- Disease management
- Laboratory tests
- Specialist visits
- Terminal care
- Adverse events

B.3.5.2 Drug acquisition costs

Fosdenopterin

Costs associated with fosdenopterin are presented in Table 39. The acquisition cost of fosdenopterin is £1,206 per 9.5mg vial. A confidential complex patient access scheme (PAS) is included in the form of a [redacted] in the model.

Patients presenting with MoCD Type A are assumed to spend the first days of life in neonatal critical care. This cost is not included in the analysis, as it is not expected to differ between treatment arms. Fosdenopterin is administered at home after the first week, prior to which it is administered in hospital and therefore incurs no additional cost. A scenario analysis explores the additional cost of neonatal critical care (£1,810; CCU13-XA01Z, NHS Reference Costs) in the fosdenopterin arm, reflecting the potential to require initial monitoring of patients following administration of fosdenopterin.(64)

Table 39. Fosdenopterin costs

Cost type	Unit cost
Fosdenopterin cost per vial (list)	£1,206
Fosdenopterin cost per vial (PAS)	£1,025

Abbreviations: PAS = patient access scheme.

A vial of fosdenopterin contains 9.5mg of product, and dose administration is based on weight. Weight data for the general population is sourced from the World Health Organisation (WHO) and is set to the [redacted] percentile in the base-case, with scenario analysis exploring the 25th percentile. Patients with MoCD Type A do not achieve normal weight due to difficulty feeding – this is demonstrated by patient-level weight data.(34-37)

Titration is based on the schedule outlined in the SmPC and is reported in Table 40.(33) The average dose for each category is applied. Vial wastage is assumed as per vial storage recommendations in the SmPC (an opened vial is to be used within 4 hours).

Table 40. Titration schedule for initial administration of fosdenopterin (33)

Schedule	Dose/day (mg/kg)	
	Age < 37 weeks	Age > 37 weeks
Initial dose	0.40	0.55
Month 1	0.70	0.75
Month 3	0.90	0.90

Abbreviations: mg = milligram; kg = kilogram.

Standard of care

Drug costs associated with SoC include medication to control seizures. Generic cost per pack was informed by the electronic market information tool (eMIT) 2022 (65) where possible, or the BNF (accessed November 2023).(66) The proportion of patients receiving BSC in the SoC arm is [redacted] and [redacted] in the fosdenopterin arm (informed by the ten most frequently used antiseizure medication at 6 months in the combined treatment and SoC arms of the study data). A simple weighted average was obtained and applied to the proportion of patients requiring SoC medication in each arm.

Table 41. Summary of SoC medication

Drug	Child dose/day[1]	Adult dose/day[1]	Cost/pack	Pack size	Mg/unit
Phenytoin	3.75 mg/kg	3.5 mg/kg	£12.46	10	250
Nitrazepam	7.5 mg	7.5 mg	£0.76	28	5
Levetiracetam	28 mg/kg	1.75 g	£20.74	10	500
Lorazepam	0.1 mg/kg	4 mg	£71.34	10	4
Diazepam	8.5 mg	8.5 mg	£0.36	28	10
Clonazepam	0.5 mg	1 mg	£12.37	105	2
Pyridoxine	10 mg	50 mg	£13.95	28	50
Valproate sodium	12.5 mg/kg	600 mg	£1.68	30	100

Midazolam	6.25 mg	10 mg	£2.37	10	5
Phenobarbital	5.63 mg	10 mg/kg	£99.96	10	200

[1]Dose/day is informed by prescribing information available from the BNF.
Abbreviations: BNF= British National Formulary; SoC= Standard of Care.

B.3.5.3 Health state unit costs and resource use

A summary of all-health-related resource use costs is presented in Table 42. Costs are taken from NHS reference costs 2021/22 unless stated otherwise.(64) The cost of a low protein diet is only applied in a scenario analysis as the efficacy of low protein diets on management of MoCD Type A is highly uncertain, and infrequently applied in clinical practice. This cost was inflated from 2015 using the CPI from the Office for National Statistics.(63)

Table 42. Healthcare resource unit costs

Cost type	Unit cost	Reference
Nasogastric feeding	£29.45	Unit cost for specialist nursing enteral feeding; nursing services, child, face-to-face.
EEG	£557	Cost for a conventional EEG, EMG or nerve conduction study, 18 years and under.
Urine test	£1.85	Unit cost for a clinical biochemistry test.
Blood test	£2.10	Unit cost for an integrated blood test
MRI	£276	Unit cost of MRI scan, one area, without contrast, 5 years and under.
CT scan	£148	Computerised Tomography Scan of One Area, without Contrast, 5 years and under.(64)
Ultrasound	£69.51	Ultrasound Scan with duration of less than 20 minutes, without Contrast
Low protein diet *	£16,740	Wilcken, B. 2015. Treatments for rare diseases: molybdenum cofactor deficiency. Inflated to 2022.(63)
Nurse visit	£57.00	PSSRU 2022, Specialist nurse band 6.(67)
Paediatrician	£224.00	Paediatrician consultant led outpatient attendance.
Neurologist	£382.16	Neurology appointment.
Emergency department	£170.46	Accident and emergency, outpatient.
Phone call follow-up	£129	Non-admitted non-face-to-face attendance, follow-up.
Dentist	£138.00	PSSRU 2022, NHS dentist – performer only. Per hour of patient contact.(67)
Hospitalisation	£956.92	Non-elective short stay, paediatric epilepsy syndrome with CC score 0.
Institutionalisation	£1,852.00	PSSRU 2022, residential homes average cost, learning disabilities.(67)
Metabolic services appointment	£549.62	Non-admitted, face-to-face, consultant led appointment. Inherited paediatric metabolic medicine services.

*Only applied in scenario analysis.
Abbreviations: CC= complications and comordbidies; CT= computerised tomography; CPI= Consumer Price

Index; EEG= electroencephalogram; EMG= electromyogram; MRI= magnetic resonance imaging; NIHR= National Institute for Health and Care Research; NHS= National Health Service.

Disease management

The proportion of patients receiving healthcare resource use was taken from the fosdenopterin and natural history data, and confirmed with [redacted], a Clinical Expert and Medical Consultant to Sentynl Therapeutics (Appendix M). [redacted] All tests were administered twice/year in the first year, and once yearly thereafter (in both arms). The proportion of patients requiring tests was taken from the SoC arm (MCD-502), as no healthcare resource use data was collected for fosdenopterin.

Table 43. Proportion of patients receiving healthcare resource use

Cost type	% patients fosdenopterin arm		% patients SoC arm	
	Year 1	Year 2+	Year 1	Year 2+
Nasogastric feeding	[redacted]	[redacted]	[redacted]	[redacted]
EEG	[redacted]	[redacted]	[redacted]	[redacted]
Urine test	[redacted]	[redacted]	[redacted]	[redacted]
Blood test	[redacted]	[redacted]	[redacted]	[redacted]
MRI	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	[redacted]	[redacted]	[redacted]	[redacted]
Ultrasound	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CT= computerised tomography; EEG= electrocardiogram; MRI= magnetic resonance imaging.

As no specialist appointments were recorded in either study (SoC or fosdenopterin), proxy data from NICE TA614 was used to estimate the number of annual specialist visits required.(68) This was reviewed by [redacted], a Clinical Expert and Medical Consultant to Sentynl Therapeutics. The number of visits were categorised by age (<12 or >12 years old) and sourced from patients having less than eight seizures per day, which is consistent with the seizure frequency observed in the MoCD Type A patient-level data (see Table 44). Frequencies were assumed equivalent between treatment arms. Clinical opinion suggested additional appointments with a metabolic physician are likely in order to prescribe fosdenopterin and monitor dose adjustments as patients grow, in collaboration with a paediatrician. Additional resource use was therefore included (Table 45).

Table 44. Frequency of specialist visits, annual

Resource type	<12 years old	≥12 years old
Nurse visit	4	2
Paediatrician	4	0
Neurologist	2	0.5
Emergency department	6	3
Phone call follow-up	2	1
Dentist	2	2
Hospitalisation	3	1.5
Institutionalisation	0%	10%

Table 45. Annual frequency of metabolic medicine appointments

Resource type	Years 1 to 3	Years 4+
Metabolic medicine services	2	1

Terminal care

A unit cost of £7,828 is applied as a one-off cost to all patients transitioning to the 'dead' state to capture end of life (i.e. palliative) costs incurred. This cost was taken from Noyes *et al.* 2013 and is inflated to 2023.(69)

B.3.5.4 Adverse reaction unit costs and resource use

Below are the costs associated with AEs taken from NHS reference costs 2021/22 (see Table 46).(64) The annual rates of a patient experiencing each AE for fosdenopterin and SoC are detailed in Table 47, taken from the patient-level data from the clinical trial programme.

Table 46. Adverse event costs

Adverse event	Cost per event	Description
General disorders and administration site condition	£852.00	Attention to Central Venous Catheter, 5 years and under.
Infections and infestations	£1,636.89	Average of Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 1+ and CC Score 0.
Gastrointestinal disorders	£3,133.38	Average of paediatric, Feeding difficulties or Vomiting, all CC scores.
Skin and subcutaneous tissue disorders	£1,777.74	Average of paediatric skin disorders, all CC scores.
Respiratory, thoracic, and mediastinal disorders	£3,550.19	Average of pleural effusions with and without interventions, all CC scores, and unspecified acute lower respiratory infections, with and without interventions, all CC scores.

Injury, poisoning, procedural complications	£852.00	Attention to Central Venous Catheter, 5 years and under.
Product issues	£852.00	
Blood and lymphatic disorders	£1,281.26	Average of Deep Vein Thrombosis, all CC scores.
Eye disorders	£1,533.00	Non-Surgical Ophthalmology without Interventions, all CC scores.
Metabolism and nutrition disorders	£2,750.62	Average of paediatric intermediate infections, all CC scores.
Nervous system disorders	£3,378.06	Average of paediatric nervous system disorders, all CC scores.
Psychiatric disorders	£324.94	Cost of a clinical consultation with a psychologist.
Surgical and medical procedures	£5,512.52	Insertion of Non-Tunnelled Central Venous Catheter, 5 years and under.
Vascular disorders	£1,281.26	Average of Deep Vein Thrombosis, all CC scores.
Cardiac disorders	£1,605.01	Non-interventional congenital cardiac conditions with CC score 0-2.
Ear and labyrinth disorders	£2,252.01	Intermediate Ear Procedures, 18 years and under.
Musculoskeletal and connective tissue disorders	£569.02	Musculoskeletal Signs or Symptoms, with CC Score 0-3.
Hepatobiliary disorders	£1,248.72	Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions, with CC Score 0-1.
Congenital, familial, and genetic disorders	£51.08	Special Screening, Examinations or Other Genetic Disorders.
Immune system disorders	£1,636.89	Average of Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 1+ and CC Score 0.
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	£1,406.48	Other or Unspecified Neoplasm, without Interventions, with CC Score 0-1.

Abbreviations: CC= complications and comorbidity.

Table 47. Annual rate, patient experiencing AEs

Adverse event	% patients fosdenopterin	% patients SoC
General disorders and administration site condition	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Injury, poisoning, procedural complications	[redacted]	[redacted]

Product issues	[redacted]	[redacted]
Blood and lymphatic disorders	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Congenital, familial, and genetic disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	[redacted]	[redacted]

Abbreviations: AEs= adverse events; SoC= standard of care.

B.3.6 Uncertainty

Long-term safety for neonates, infants and children has been documented in clinical trials with fosdenopterin. Due to the rarity of the disease, small size of study population, and short follow-up period, there is currently limited long-term safety data available, particularly for adolescents and adults. Therefore, to consolidate the safety profile and gain further information about the medicine, there is a need to gather long-term safety data from all patients receiving or who have received fosdenopterin.

A key limitation is the paucity and/or absence of other data, notably:

- Small patient numbers and lack of long-term efficacy data
- Absence of QoL data specifically in MoCD Type A
- Absence of complete healthcare resource use data

In order to fill these data gaps, the best available data were selected. An appropriate proxy disease, Dravet syndrome, was used, which was confirmed by [redacted], a Clinical Expert and Medical Consultant to Sentynl Therapeutics to be a suitable equivalent to estimate QoL and missing resource use. Other assumptions were informed by clinical opinion, such as applying general population QoL to treated patients in the long-term and the extrapolation of long-term survival. A NICE technology appraisal was used to fill gaps in the absence of MoCD Type A healthcare resource use data (TA614, cannabidiol for treating seizures associated with Dravet syndrome).(68) Long-term outcomes of safety and

effectiveness such as survival, AEs, growth, and feeding status were included in the data collection plan and will contribute to the development of more robust model inputs. In the meantime, scenarios were implemented where possible.

The uncertainty present in the model was explored using sensitivity and scenario analyses, specifically in key drivers of cost-effectiveness, which allows exploration of the impact of a more conservative base-case. All parametric models are presented in the survival extrapolations, and a scenario is presented excluding late-onset patients.

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

B.3.7.2 Summary of variables applied in the economic model

A summary of the base-case cost-effectiveness analysis inputs is provided in Table 48.

Table 48. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General settings			
Time horizon (years)	100	Not varied	Section B.3.2
Discount rate (costs and benefits)	3.5%		
Cycle length (years)	4 weeks		
Baseline age	0.00		
Sex (% cohort female)	30.59%	Beta; 0.28 – 0.34	
Patient weight band	[redacted] percentile	Not varied	
Discontinuation rate of Nulibry	0.0	Beta; 0 – 0.05	Section B.3.3.4
Utility in dead patients	0.0	NA; 0 – 0	Section B.3.4
EQ-5D, age 0-1	0.33	Norma	
EQ-5D, age 2-5	0.46	Norma	
EQ-5D, age 6-11	0.43	Normal	
EQ-5D, age 12-17	0.43	Normal	
EQ-5D, age 18-100	0.34	Normal	
Utility Loss in Carers	-0.140	Beta; -0.13 – -0.15	
Number of Carers - fosdenopterin	1.0	Gamma; 0.9 – 1.1	
Number of Carers -SoC	1.8	Gamma; 1.62 – 1.98	
Cost of fosdenopterin	£1,205.5	Not varied	Section B.3.5.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Nasogastric feeding Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	Section B.3.5.3
Low protein diet proportion - fosdenopterin - Y1	0%	Beta; 0 – 0	
EEG Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	
Urine tests Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	
Blood tests Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	
MRI Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	
CT scan Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	
Ultrasound Proportion - fosdenopterin - Y1	[redacted]	Beta; [redacted]	
Nasogastric feeding Proportion - SoC - Y1	[redacted]	Beta; [redacted]	
Low protein diet proportion - SoC - Y1	0%	Beta; 0 – 0	
EEG Proportion - SoC - Y1	[redacted]	Beta; [redacted]	
Urine tests Proportion - SoC - Y1	[redacted]	Beta; [redacted]	
Blood tests Proportion - SoC - Y1	[redacted]	Beta; [redacted]	
MRI Proportion - SoC - Y1	[redacted]	Beta; [redacted]	
Nasogastric feeding Proportion - fosdenopterin - Y2	[redacted]	[redacted]	
Low protein diet proportion - fosdenopterin - Y2	[redacted]	[redacted]	
EEG Proportion - fosdenopterin - Y2	[redacted]	Beta[redacted]	
Urine tests Proportion - fosdenopterin - Y2	[redacted]	Beta; [redacted]	
Blood tests Proportion - fosdenopterin - Y2	[redacted]	Beta; [redacted]	
MRI Proportion - fosdenopterin - Y2	[redacted]	Beta; [redacted]	
Nasogastric feeding Proportion - SoC - Y2	[redacted]	Beta; [redacted]	
Low protein diet proportion - soc - Y2	[redacted]	Beta; 0 – 0	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
EEG Proportion - SoC - Y2	[redacted]	Beta; [redacted]	
Urine tests Proportion - SoC - Y2	[redacted]	Beta; [redacted]	
Blood tests Proportion - SoC - Y2	[redacted]	Beta; [redacted]	
MRI Proportion - SoC - Y2	[redacted]	Beta; [redacted]	
Nasogastric feeding Annual Frequency - fosdenopterin - Y1	[redacted]	[redacted]	
EEG Annual Frequency - fosdenopterin - Y1	[redacted]	[redacted]	
Urine tests Annual Frequency - fosdenopterin - Y1	[redacted]	[redacted]	
Blood tests Annual Frequency - fosdenopterin - Y1	[redacted]	[redacted]	
MRI Annual Frequency - fosdenopterin - Y1	[redacted]	[redacted]	
Nasogastric feeding Annual Frequency - fosdenopterin - Y2	[redacted]	[redacted]	
EEG Annual Frequency - fosdenopterin - Y2	[redacted]	[redacted]	
Urine tests Annual Frequency - fosdenopterin - Y2	[redacted]	[redacted]	
Blood tests Annual Frequency - fosdenopterin - Y2	[redacted]	[redacted]	
MRI Annual Frequency - fosdenopterin - Y2	[redacted]	[redacted]	
Nasogastric feeding Annual Frequency - SoC - Y1	[redacted]	[redacted]	
EEG Annual Frequency - SoC - Y1	[redacted]	[redacted]	
Urine tests Annual Frequency - SoC - Y1	[redacted]	[redacted]	
Blood tests Annual Frequency - SoC - Y1	[redacted]	[redacted]	
MRI Annual Frequency - SoC - Y1	[redacted]	[redacted]	
Nasogastric feeding Annual Frequency - SoC - Y2	[redacted]	[redacted]	
EEG Annual Frequency - SoC - Y2	[redacted]	[redacted]	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Urine tests Annual Frequency - SoC - Y2	[redacted]	[redacted]	
Blood tests Annual Frequency - SoC - Y2	[redacted]	[redacted]	
MRI Annual Frequency - SoC - Y2	[redacted]	[redacted]	
Nasogastric feeding cost	29.5	Gamma; 26.51 – 32.4	
EEG cost	557.0	Gamma; 501 – 613	
Urine tests cost	1.8	Gamma; 1.665 – 2.035	
Blood tests cost	2.1	Gamma; 1.89 – 2.31	
MRI cost	275.6	Gamma; 248 – 303	
Terminal care cost (Death)	7828.3	Gamma; 7045 – 8611	
Administration hospitalisation cost	1809.6	Gamma; 1629 – 1991	
Nurse visit, <12 years old annual visits	4.0	Gamma; 3.6 – 4.4	
Nurse visit, >12 years old annual visits	2.0	Gamma; 1.8 – 2.2	
Paediatrician visit, <12 years old annual visits	4.0	Gamma; 3.6 – 4.4	
Paediatrician visit, >12 years old annual visits	0.0	Gamma; 0 – 0	
Neurologist visit, <12 years old annual visits	2.0	Gamma; 1.8 – 2.2	
Neurologist visit, >12 years old annual visits	0.5	Gamma; 0.45 – 0.55	
Emergency department visit, <12 years old annual visits	6.0	Gamma; 5.4 – 6.6	
Emergency department visit, >12 years old annual visits	3.0	Gamma; 2.7 – 3.3	
Phone call follow-up, <12 years old annual visits	2.0	Gamma; 1.8 – 2.2	
Phone call follow-up, >12 years old annual visits	1.0	Gamma; 0.9 – 1.1	
Dentist visit, <12 years old annual visits	2.0	Gamma; 1.8 – 2.2	
Dentist visit, >12 years old annual visits	2.0	Gamma; 1.8 – 2.2	
Hospitalisation, <12 years old annual visits	3.0	Gamma; 2.7 – 3.3	
Hospitalisation, >12 years old annual visits	1.5	Gamma; 1.35 – 1.65	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Institutionalisation, <12 years old proportion	0.0	Beta; 0 – 0	
Institutionalisation, >12 years old proportion	0.1	Beta; 0.09 – 0.11	
Cost of a nurse visit	£55.00	Gamma; 50 – 61	
Cost of a paediatrician visit	£224.00	Gamma; 202 – 246	
Cost of a neurologist visit	£382.16	Gamma; 344 – 420	
Cost of an emergency department visit	£170.46	Gamma; 153 – 188	
Cost of a phone call follow-up	£129.00	Gamma; 116 – 142	
Cost of a dentist visit	£133.00	Gamma; 120 – 146	
Cost of a hospitalisation	£956.92	Gamma; 861 – 1053	
Cost of institutionalisation	£1,214.00	Gamma; 1093 – 1335	
Fosdenopterin - infections and infestations frequency	[redacted]	Beta[redacted]	
Fosdenopterin - general disorders and administration site condition frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - respiratory, thoracic, and mediastinal disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - gastrointestinal disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - metabolism and nutrition disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - product issues frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - nervous system disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - psychiatric disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - skin and subcutaneous tissue disorders frequency	[redacted]	Beta; [redacted]	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Fosdenopterin - surgical and medical procedures frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - vascular disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - cardiac disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - ear and labyrinth disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - musculoskeletal and connective tissue disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - hepatobiliary disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - congenital, familial and genetic disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - immune system disorders frequency	[redacted]	Beta; [redacted]	
Fosdenopterin - neoplasms benign, malignant, and unspecified (incl cysts and polyps) frequency	[redacted]	Beta; [redacted]	
SoC - infections and infestations frequency	[redacted]	Beta; [redacted]	
SoC - general disorders and administration site condition frequency	[redacted]	Beta; [redacted]	
SoC - respiratory,thoracic, and mediastinal disorders frequency	[redacted]	Beta; [redacted]	
SoC - gastrointestinal disorders frequency	[redacted]	Beta; [redacted]	
SoC - metabolism and nutrition disorders frequency	[redacted]	Beta; [redacted]	
SoC - product issues frequency	0.00%	Beta; 0 – 0	
SoC - nervous system disorders frequency	[redacted]	Beta; [redacted]	
SoC - psychiatric disorders frequency	[redacted]	Beta; [redacted]	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
SoC - skin and subcutaneous tissue disorders frequency	[redacted]	Beta; [redacted]	
SoC - surgical and medical procedures frequency	[redacted]	Beta; [redacted]	
SoC - vascular disorders frequency	[redacted]	Beta; [redacted]	
SoC - cardiac disorders frequency	[redacted]	Beta; [redacted]	
SoC - ear and labyrinth disorders frequency	[redacted]	Beta; [redacted]	
SoC - musculoskeletal and connective tissue disorders frequency	[redacted]	Beta; [redacted]	
SoC - hepatobiliary disorders frequency	[redacted]	Beta; [redacted]	
SoC - congenital, familial, and genetic disorders frequency	[redacted]	Beta; [redacted]	
SoC - immune system disorders frequency	[redacted]	Beta; [redacted]	
SoC - neoplasms benign, malignant and unspecified (incl cysts and polyps) frequency	[redacted]	Beta; [redacted]	
Infections and infestations cost	£1,637	Gamma; 1473 – 1801	
General disorders and administration site condition cost	£852	Gamma; 767 – 937	
Respiratory, thoracic, and mediastinal disorders cost	£3,550	Gamma; 3195 – 3905	
Gastrointestinal disorders cost	£3,133	Gamma; 2820 – 3447	
Metabolism and nutrition disorders cost	£2,751	Gamma; 2476 – 3026	
Product issues cost	£852	Gamma; 767 – 937	
Nervous system disorders cost	£3,378	Gamma; 3040 – 3716	
Psychiatric disorders cost	£325	Gamma; 292 – 357	
Skin and subcutaneous tissue disorders cost	£1,778	Gamma; 1600 – 1956	
Surgical and medical procedures cost	£5,513	Gamma; 4961 – 6064	
Vascular disorders cost	£1,281	Gamma; 1153 – 1409	
Cardiac disorders cost	£1,605	Gamma; 1445 – 1766	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Ear and labyrinth disorders cost	£2,252	Gamma; 2027 – 2477	
Musculoskeletal and connective tissue disorders cost	£569	Gamma; 512 – 626	
Hepatobiliary disorders cost	£1,249	Gamma; 1124 – 1374	
Congenital, familial, and genetic disorders cost	£51	Gamma; 46 – 56	
Immune system disorders cost	£1,637	Gamma; 1473 – 1801	
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) cost	£1,406	Gamma; 1266 – 1547	
Infections and infestations disutility	-0.002	Beta; -0.002 – -0.003	Section B.3.4.4
General disorders and administration site condition disutility	-0.002	Beta; -0.002 – -0.003	
Respiratory, thoracic, and mediastinal disorders disutility	-0.034	Beta; -0.03 – -0.037	
Gastrointestinal disorders disutility	-0.051	Beta; -0.046 – -0.056	
Metabolism and nutrition disorders disutility	-0.084	Beta; -0.076 – -0.092	
Product issues disutility	-0.002	Beta; -0.002 – -0.003	
Nervous system disorders disutility	-0.070	Beta; -0.063 – -0.076	
Psychiatric disorders disutility	-0.101	Beta; -0.091 – -0.111	
Skin and subcutaneous tissue disorders disutility	-0.001	Beta; -0.001 – -0.001	
Surgical and medical procedures disutility	-0.002	Beta; -0.002 – -0.003	
Vascular disorders disutility	-0.053	Beta; -0.048 – -0.058	
Eye disorders disutility	-0.009	Beta; -0.008 – -0.01	
Injury, poisoning, procedural complications disutility	-0.051	Beta; -0.046 – -0.056	
Cardiac disorders disutility	-0.025	Beta; -0.022 – -0.027	
Ear and labyrinth disorders disutility	-0.010	Beta; -0.009 – -0.011	

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Musculoskeletal and connective tissue disorders disutility	-0.063	Beta; -0.057 – -0.069	
Hepatobiliary disorders disutility	-0.058	Beta; -0.052 – -0.064	
Congenital, familial, and genetic disorders disutility	-0.005	Beta; -0.004 – -0.005	
Immune system disorders disutility	-0.056	Beta; -0.05 – -0.061	
Neoplasms benign, malignant, and unspecified (including cysts and polyps) disutility	-0.009	Beta; -0.008 – -0.009	

Abbreviations: Y1= year 1; Y2= year 2; SoC= Standard of Care; MRI= Magnetic resonance imaging

B.3.7.3 Assumptions

A list of assumptions used in the economic model is provided in Table 49.

Table 49. Assumptions of the economic analysis

Assumptions	Chosen methodology	Justification
Weight	[redacted] percentile used	Patients were assumed to be of lower weight.
Utilities	QoL data was not collected in the study programme for fosdenopterin. The QoL SLR did not reveal any direct sources for utilities in MoCD Type A for use in the model. Therefore, a proxy from Dravet syndrome was applied in the model.(56)	Proxy utilities from Dravet were considered the most reliable in the absence of published quality of life data in MoCD Type A.Consultation with a clinical expert suggested that early treatment with fosdenopterin would result in long-term utilities that are comparable to the general population (Appendix M).
Parametric models	Long-term survival probabilities were estimated using independent parametric models	To estimate long-term survival probabilities, parametric models were developed for survival data for both SoC and fosdenopterin arms, using a range of parametric distributions in accordance with NICE TSD14 guidance.(43)
Early-onset population	Survival probabilities were re-calculated using only data for patients with early-onset of MoCD Type A; that is, patients who presented with their first signs and symptoms within 28 days of birth. In total, four individuals were excluded from the SoC arm (enrolled in MCD-502), and no	Fosdenopterin has shown positive effects on gross motor function, with treated patients (particularly those the early-onset form of the disease) exhibiting better motor function.

	patients were excluded from the treatment arm.	
Treatment discontinuation	For the economic analyses, treatment discontinuation was not considered in the models as clinical consultation suggested patients were not anticipated to discontinue treatment due to the severity of MoCD Type A, except where a patient's prognosis of survival was extremely poor.	Clinical validation

Abbreviations: MoCD= molybdenum cofactor deficiency; QoL= quality of life; SoC= standard of care.

B.3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

Aggregated base-case results of the cost-effectiveness model are reported in Table 50. Disaggregated results are presented in Table 51 and Table 51. At list price, the base-case ICER is £1,971,011. With PAS [redacted]) the ICER is [redacted]. Given the undiscounted QALYs gained in the fosdenopterin arm (36.77 excluding caregiver utilities), fosdenopterin qualifies for a cost-effectiveness threshold of £300,000.

Discounted life-years gained are 18.13 on the fosdenopterin arm and 6.37 in the SoC arm, resulting in an incremental LY gain of 11.76 and an incremental QALY gain of 18.13. This is an exceptional outcome, as there is currently no effective treatment for MoCD Type A, and fosdenopterin is the only prospective treatment which offers real survival and QoL benefits for patients. The large incremental QALYs accumulated reflect not only the expected survival benefit of fosdenopterin, but also the QoL improvements that are anticipated in the long-term.

Model results are primarily driven by the large survival gain accrued in the fosdenopterin arm, as patients in the SoC arm only accrue 6.37 LYs over the lifetime horizon, vs 18.13 LYs in the fosdenopterin arm. Another key model driver and major cost component is the acquisition cost of fosdenopterin, as patients are required to take the medicine for their lifetimes and the relative cost of SoC medicine is negligible.

Table 50. Base-case results

	Fosdenopterin	SoC	Incremental
Total costs (list price)	£35,875,538	£143,530	£35,732,008
Total costs (PAS)	[redacted]	£143,530	[redacted]
Total QALYs	27.59	9.47	18.13
ICER (list price)			£1,971,011
ICER (PAS)			[redacted]

Abbreviations: ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years; SoC= standard of care.

Table 51. Disaggregated costs

	Fosdenopterin	SoC	Incremental
Undiscounted			
Drug acquisition	£99,012,834	£1,857	£99,010,977
Drug acquisition (PAS)	[redacted]		[redacted]
Disease management	£418,641	£167,882	£250,759
Adverse events	£199	£37	£162
Terminal care	£221,337	£309,896	-£88,559
Total undiscounted	**£99,653,011**	**£479,672**	**£99,173,339**
Total undiscounted (PAS)	[redacted]	**£479,672**	[redacted]
Discounted			
Drug acquisition	£35,672,674	£1,120	£35,671,554
Drug acquisition (PAS)	[redacted]		[redacted]
Disease management	£189,306	£105,310	£83,996
Adverse events	£89	£29	£60
Terminal care	£13,470	£37,070	-£23,601
Total discounted	**£35,875,538**	**£143,530**	**£35,732,008**
Total discounted (PAS)	[redacted]	**£143,530**	[redacted]

Abbreviations: ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years; SoC= standard of care.

Table 52: Disaggregated outcomes

	Fosdenopterin	**SoC**	**Incremental**
Undiscounted			
LYs	40.59	8.20	32.39
QALYs	36.19	1.36	34.83
Discounted			
LYs	18.13	6.37	11.76
QALYs	27.59	9.47	18.13

Abbreviations: ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years; SoC= standard of care; LY= life-years.

B.3.8.2 Net health benefit

The net monetary benefit for fosdenopterin vs SoC is presented below.

Table 53: Net monetary benefit

	Value

Incremental QALYs	18.13
Incremental costs	£35,732,008
Incremental costs (PAS)	[redacted]
Net monetary benefit	-£30,293,378
Net monetary benefit (PAS)	[redacted]

Abbreviations: QALYs = quality-adjusted life-years.

B.3.9 Exploring uncertainty

B.3.9.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken for rigorous assessment of uncertainty surrounding the point estimates. Monte Carlo simulations were used to vary parameter inputs stochastically. By sampling all model parameters using 1,000 replications of varying point estimates (ICERs), a four-quadrant cost-effectiveness plane was constructed, illustrating four feasible conclusions regarding the cost-effectiveness of fosdenopterin relative to SoC. The probabilistic ICER is [redacted], which represents only a 0.64% decrease from the deterministic ICER and demonstrates that the uncertainty present in the model has been controlled and accounted for. The ICER scatterplot of the 1,000 simulations is presented in **Error! Reference source not found.** and the cost-effectiveness acceptability curve is presented in **Error! Reference source not found.**. With a PAS of [redacted], the probability of cost-effectiveness is [redacted] at a willingness to pay (WTP) threshold of [redacted] gained (Table 55).

Table 54. Results from the PSA

	Fosdenopterin	SoC	Incremental	% change from deterministic ICER
Total costs	[redacted]	£148,144	[redacted]	-0.05%
Total QALYs	27.57	9.49	18.08	-0.29%
ICER			[redacted]	-0.64%

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; SoC, standard of care.

[redacted]

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years.

Table 55. Proportion of simulations cost-effective

Threshold	% simulations cost-effective with PAS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: PAS, patient access scheme.

[redacted]

Abbreviations: PAS, patient access scheme; PSA, probabilistic sensitivity analysis

B.3.9.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis was performed to examine the impact on the ICER for upper and lower bounds of included parameters. This was done through an automated one-way sensitivity analysis programme built for the model. A tornado diagram is presented in **Error! Reference source not found.**, and upper and lower bounds for the ten most influential parameters are reported in Table 56.

[redacted]

Table 56. Upper and lower bounds from one-way sensitivity analysis

Parameter	Range	ICER at lower bound	ICER at upper bound
Annual discount rate - costs (%)	[0.000 - 0.050]	[redacted]	[redacted]
Annual discount rate - benefits (%)	[0.000 - 0.050]	[redacted]	[redacted]
Model time horizon (years)	[10.000 - 100.000]	[redacted]	[redacted]
Discontinuation rate of Nulibry	[0.000 - 0.050]	[redacted]	[redacted]
Patient characteristics - weight	[1.000 - 3.000]	[redacted]	[redacted]
Cost Nulibry	[redacted]	[redacted]	[redacted]
Parametric survival distribution - Include background mortality from lifetables	[FALSE - TRUE]	[redacted]	[redacted]

Apply caregiver disutilities	[FALSE - TRUE]	[redacted]	[redacted]
Joint survival models	[FALSE - TRUE]	[redacted]	[redacted]
Number of Carers -SoC	[1.620 - 1.980]	[redacted]	[redacted]
Utility Loss in Carers	[-0.126 - -0.154]	[redacted]	[redacted]
Number of Carers - fosdenopterin	[0.900 - 1.100]	[redacted]	[redacted]
Patient characteristics -	% female [0.275 - 0.337]	[redacted]	[redacted]
Include KM data	[FALSE - TRUE]	[redacted]	[redacted]
Apply AE disutilities	[FALSE - TRUE]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care; KM, Kaplan-Meier; AE, Adverse event.

B.3.9.3 Scenario analysis

Scenario analyses were conducted to analyse what impact different assumptions regarding model structure, treatment practice, utility values, could have on the results. Several scenarios were created to test the robustness of the ICER. The results of the scenario analysis are reported in Table 57. Varying the time horizon and discount rate had the largest impact on the ICER (-54% to +24%).

Table 57. Results from scenario analysis

Scenario	ICER	% change from base-case
Apply KM + parametric model	[redacted]	-18.64%
Joint models (log-logistic)	[redacted]	-3.75%
25th percentile weight	[redacted]	9.31%
Discount rate=0%	[redacted]	23.78%
Discount rate=5%	[redacted]	-12.44%
Time horizon = 5 years	[redacted]	-53.32%
Time horizon = 10 years	[redacted]	-54.14%
Caregiver disutilities excluded	[redacted]	7.02%
Low protein diet included	[redacted]	-3.75%
Early-onset population (N=33)	[redacted]	-3.75%
Discontinuation of fosdenopterin = 1% annual	[redacted]	-2.32%
Long-term fosdenopterin QoL = 50% equivalent of general population	[redacted]	-3.75%
Disutility of caregivers = -0.05	[redacted]	2.91%

Abbreviations: ICER, incremental cost-effectiveness ratio; KM; Kaplan-Meier; QoL, quality of life; SoC, standard of care.

B.3.10 Subgroup analysis

No subgroup analysis was performed in the economic evaluation. Although subgroup analyses are presented as part of the clinical data there was no rationale for presenting an economic analysis on specific cohorts. A scenario is presented excluding the late-onset population of the clinical trial (N=33).

B.3.11 Benefits not captured in the QALY calculation

The use of fosdenopterin will result in substantial health-related benefits which will not be included in the QALY calculation.

The impact of caring for a patient with MoCD Type A treated with SoC include reduction in productivity, levels or work and financial stability, as well as quality of sleep for carers. In addition to this, carers may experience anxiety and depression due to the worry of their child being so unwell, and the high possibility that they may die soon. It is unlikely that this will be included in the QALY calculation.

The primary indicated benefit of treatment with fosdenopterin is improved patient survival. MoCD Type A is also characterised by the incidence of seizures, difficulty feeding, and compromised mobility. Treatment with fosdenopterin is primarily anticipated to impact survival but is also expected to limit the progression of these symptoms (i.e., a stabilisation in the incidence of seizures, a reduced need for nasogastric feeding and a higher likelihood of gross motor skill preservation), which is correlated to the time of treatment. This means that parents will potentially be at least somewhat relieved of their caregiving duties when the child is able to attend school.

B.3.12 Validation

B.3.12.1 Validation of cost-effectiveness analysis

Internal quality assurance measures were undertaken throughout the model development. The model was validated using extreme values and formula auditing to ensure the consistency of model estimates.

The model structure and inputs were critiqued and validated by a clinician and health economics consultant. Where appropriate, any errors were amended. Overall, the

validation identified no issues with the structural or computational accuracy of the model.

B.3.13 Interpretation and conclusions of economic evidence

This economic evaluation presents the cost-effectiveness of fosdenopterin vs SoC and is the first attempt at parameterising an economic model in this condition. In the base-case, the ICER for fosdenopterin vs SoC is £1,971,011, which represents 18.13 incremental QALYs and £35,732,008 in incremental costs. With the PAS, the ICER is [redacted] in incremental costs). The ICER in the probabilistic analysis resulted in an ICER of [redacted] with the PAS, which is congruent with the deterministic analysis and demonstrates the limited extent of uncertainty in the model.

B.3.14 Cost to the NHS and Personal Social Services

Patient numbers

The number of patients in England and Wales with MoCD Type A was one in 2023, with an incidence of 0.0003% (10), which meets the HST prevalence criteria.(70) Assuming an annual population growth of 0.05%, this results in an estimate of 1.77 patients by 2028. A summary of patient numbers (including incidence and prevalence) is detailed in Table 58.

Table 58. Summary of patient numbers

Parameters	Value	Source
Prevalence	1 patient	Number of patients in England (2023)
Incidence	0.0003%	Based on evidence.(10)
Percent covered by payer	100%	Assumption

Costs

The annual cost of fosdenopterin is based on weight. Assuming a baseline weight calculated from the [redacted] percentile of patients, a weighted average cost per year is calculated using an acquisition cost per vial of £1,206 in the base-case and [redacted] at PAS price. The dose accounts for the number of vials per day in Year 1 and 2 compared with that in Years 3 to 5.

An average annual cost of £831.32 is estimated for SoC, using average doses for all comparators (in equal doses to cost-effectiveness model calculations). The total cost

of treatment without and with fosdenopterin, at list price and PAS price, is presented in Table 59 and Table 60. Market share is expected to be 100% for fosdenopterin from year 1, onwards.

Table 59. Total cost of treatment without fosdenopterin

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
Fosdenopterin	£0	£0	£0	£0	£0
SoC	£759	£1,949	£2,844	£3,444	£3,802
Total	£759	£1,949	£2,844	£3,444	£3,802

Abbreviations: SoC=standard of care.

Table 60. Total cost of treatment with fosdenopterin

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
Fosdenopterin	£529,158	£1,394,975	£4,260,086	£5,481,717	£6,477,869
Fosdenopterin (PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	£0	£0	£0	£0	£0
Total	£528,399	£1,393,025	£4,257,242	£5,478,273	£6,474,067
Total (PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS=patient access scheme; SoC=standard of care.

Results of the budget impact model (BIM)

The total budget impact for fosdenopterin at is provided in Table 61 for the introduction of fosdenopterin across 5 years. Fosdenopterin is not expected to exceed the budget impact test of £20 million at 3 or 5 years.

Table 61. Total budget impact with PAS

	Year 1	Year 2	Year 3	Year 4	Year 5
Total/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total/patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No additional costs are anticipated relating to the introduction of fosdenopterin, as regular monitoring is already in place for patients on SoC and is not expected to change dramatically as a result of additional treatment. Productivity losses have not been quantified in the BIM but are likely to result in a wider societal saving.

Additionally, as mentioned in the cost section, the budget impact does not capture the wider societal costs, such as increased productivity. The true budget impact is therefore likely to vary from those presented here.

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B.5 Appendices

Appendix C. Summary of product characteristics (SmPC) and UK public assessment report

Please see document ‘Appendix C_SmPC’ and ‘Appendix C_EMA EPAR’.

Appendix D. Identification, selection and synthesis of clinical evidence

Appendix D.1. Identification and selection of relevant studies

Please see ‘Appendix D.1_ MoCD Type A clinical safety SLR_November 2023 update’.

Appendix D.2. Participant flow in the relevant randomised control trials

Please see Section B.2.4.2 of the main submission document.

Appendix D.3. Critical appraisal for each study

Please see ‘Appendix D.1_ MoCD Type A clinical safety SLR_November 2023 update’.

Appendix E. Subgroup analysis

Included in the main submission document, please see section B.2.7.

Appendix F. Adverse reactions

Included in the main submission document, please see section B.10.

Appendix H. Health-related quality of life studies

Please see ‘Appendix H_MoCD Type A health state utilities SLR_November 2023 update’.

Appendix J. Clinical outcomes and disaggregated results from the model

Included in the main submission document, please see Section B.3.8.

Appendix K. Price details of treatments included in the submission

Please see ‘Appendix K_ Price details of treatments included in the submission’.

Appendix L. Checklist of confidential information

Please see ‘Appendix L_Checklist of confidential information’.

Appendix M. Clinical opinion

Please see ‘Appendix M_CEM input validation’.

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open access IJTAHC journal article.

Notes for authors: Please complete the template using plain language, taking time to explain all scientific terminology. As you draft your response, please do not delete the intro text included in each section. It might be a useful reference for patient reviewers.

However, any text preceded by the words 'Notes for authors' simply contains additional prompts for the company to advise them on the type of information that may be most relevant, and the level of detail they need to include. You may delete this text where indicated.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic name: Fosdenopterin Brand name: Nulibry®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Fosdenopterin is intended for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A. (1)

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 15 September 2022, the European Medicines Agency (EMA), a regulatory body that ensures the safety, effectiveness, and quality of drugs before they can be sold and used in EU countries, approved fosdenopterin to be used for the treatment of MoCD Type A, under “exceptional circumstances,” which means that the disease is so rare that it is difficult to gather the usual full information about how effective and safe a medicine is. The assessment report for the approval can be found here: https://www.ema.europa.eu/en/medicines/human/EPAR/nulibry

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

There are no existing collaborations between the pharmaceutical company and patient groups.

Section 2: current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the main indication (condition and the population who would use the treatment) being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen. You may delete this note text.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to

the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

MoCD Type A is an inherited disorder that affects the natural chemical processes needed for your body to work (metabolism). Signs of this disorder metabolism usually appear shortly after birth and include feeding difficulties and seizures. Other signs are a decreased awareness or reaction to the environment, a high-pitched cry, an increase in startle reactions to a sudden event such as sound or movement, and weak or stiff muscles.(2-4)

MoCD Type A results from an error in the gene called *MOCS1*. This interferes with the body making an essential substance called cyclic pyranopterin monophosphate (cPMP).(5) When this substance is missing, certain compounds (sulphites) that are formed in the body, cannot be broken down (6, 7). These compounds are toxic to the brain and can negatively affect or delay the development of a child. (8-11)

MoCD Type A is life-threatening and presents serious patient and caregiver challenges, as patients have difficulty feeding, sitting, and speaking. Some patients are bedridden and unable to walk at all.(8, 12, 13) In the absence of treatment, patients usually only survive through the first years of life.(11)

There is a high burden associated with giving care to patients suffering with MoCD. Caregivers must manage seizures that continue throughout their child's life and adapt as the child fails to meet developmental milestones and suffers from physical and issues with learning and mental processes.(14) All these factors are time-consuming and expensive, and in most cases will leave caregivers little time to focus on other aspects of their life such as having a career or looking after their other children.(15)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

When symptoms of MoCD Type A present, patients suspected of having the disease can be diagnosed by testing for changes in important biochemical markers of disease such as falling or a decrease in plasma or urinary uric acid, and an increase in urinary s-sulphocysteine (SSC) and xanthine.(7, 13) Genetic testing can then be used to confirm diagnosis.(11)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

> What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
> Please also consider:
> if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
> are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Most patients with MoCD Type A develop symptoms in the first few days of life, with few surviving early childhood.(10, 11) Current treatments for MoCD Type A focus on relieving symptoms associated with the disease, or supportive care for the patient (8, 11, 16-20). Current treatments include antiepileptic medications and special diets, but these have shown little benefit. Although antiepileptic medications may provide short-term relief, they do not address the build-up of brain damaging sulphites within the brain (the primary cause of the symptoms associated with MoCD). Patients usually must be fed through a feeding tube as they are unable to eat by mouth.(11)

Current treatments attempt to control the worsening symptoms, but not the disease itself. Seizures are difficult to control even with medication, the likelihood of survival is still poor, and the brain damage and development issues continue worsen. There is therefore a high unmet need for a treatment to prevent the brain and central nervous system damage that MoCD Type A causes, as none are currently approved in England.

2d) Patient-based evidence (PBE) about living with the condition

Context:

> Patient-based evidence (PBE) is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and

carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about patient needs and disease experiences. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patient-based evidence of the experiences associated with MoCD Type A has not been collected.

Section 3: the treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly. You may delete this note text.

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Fosdenopterin provides the missing substance, cPMP, that the body needs to break down the harmful sulphite compounds associated with the condition.(21) Fosdenopterin is novel because the current standard of care is used to treat the symptoms, rather than the cause of the disease.(21) Fosdenopterin has been given ‘Orphan’ status by the EMA because it is intended to treat a rare, life-threatening and life-long disease.(22) Fosdenopterin was given EMA approval in September 2022, making it the first medicine approved in Europe to treat patients with MoCD Type A. The efficacy and safety of fosdenopterin are supported by data from 15 treated patients, compared to 37 untreated, ‘natural history’ patients.(23-26) Treatment with fosdenopterin demonstrated a large improvement in survival, feeding, growth, developmental assessments, disease biomarkers (signs or indicators that can tell

us something about a disease). The introduction of fosdenopterin to clinical practice will represent a life-saving and meaningful improvement for MoCD Type A patients, as the therapy significantly improves survival and has the potential to improve patient and caregiver wellbeing.(23-26)

Please see the link below to access the summary of product characteristics for fosdenopterin:

https://www.ema.europa.eu/en/documents/product-information/nulibry-epar-product-information_en.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐Yes

☒No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Fosdenopterin is injected into a vein through an intravenous access line or port (catheter). A doctor who is experienced in the management of these inherited genetic disorders will start and supervise the treatment with fosdenopterin. Fosdenopterin can be given at home. Before treatment is used at home for the first

time, a doctor or nurse will train the caregiver in how to prepare the medicine and give the patient a dose of fosdenopterin.

The medicine should always be used exactly as the doctor or nurse has instructed. The dose depends on the patient's age and body weight, and the dose will need to be given once each day. The doctor will work out the dose that is needed.

Please see the patient information leaflet for more information on how to take fosdenopterin: https://www.ema.europa.eu/en/documents/product-information/nulibry-epar-product-information_en.pdf

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Several clinical studies have been completed to support the authorisation of fosdenopterin in Europe. One study involved a substance called recombinant cPMP (rcPMP) in study MCD-501, and two studies involved fosdenopterin (cPMP), MCD-201 and MCD-202. Both rcPMP and fosdenopterin have the same active ingredient, so they are expected to work the same way and are the same in terms of treatment. These studies looked at factors such as disease biomarkers, survival rates, seizure activity, feeding, development, and brain examinations to gather information on how effective and safe the treatment is.

An additional study, MCD-502, was completed to collect past data and create a group of participants not treated with the new medication for comparison.

Studies were carried out across Germany, Israel, the Netherlands, Tunisia, Turkey, the UK and the US.

- **MCD-501:** This study tested ten children with MoCD Type A to see how they responded to treatment with rcPMP, which is considered the same, chemically, as fosdenopterin. The study included participants with MoCD Type A, suspected Type A, or Type B who had previously received rcPMP. The study was completed in 2014.
- **MCD-201:** This study tested fosdenopterin in eight children with MoCD Type A who had previously been treated with rcPMP. The study looked at how safe and effective the medication was, as well as how the body absorbed, delivered, and removed the drug, and how the drug affected the body. The study was completed in 2022.

- **MCD-202:** This study tested fosdenopterin in patients who had not been previously treated with rcPMP. The study included three participants with a confirmed diagnosis of MoCD based on doctor's observations, lab tests, or a genetic test. The study was completed in 2022.
- **MCD-502:** This study followed 37 children with MoCD Type A to learn more about how the disease naturally progresses. The study was completed in 2015.

The main evidence supporting the application comes from analysing data from the studies, comparing the treated patients with a group of patients with MoCD Type A with similar patient characteristics who were not treated with fosdenopterin) from the natural history study, MCD-502. The analysis involved 15 patients treated with fosdenopterin or rcPMP compared to 37 untreated individuals.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

> Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Fosdenopterin significantly improves overall survival for patients with MoCD Type A

People who received fosdenopterin survived longer than those who did not. For those treated, 13.3% died, compared to 64.9% of untreated individuals. The untreated group's chances of dying were 5.5 times higher than the treated group. At one year of age, 93.3% of treated individuals were alive, compared to 75.3% of untreated individuals.(27)

Improvements in urinary biomarkers related to the disease

Fosdenopterin quickly reduced certain urinary biomarkers related to the disease. These positive changes were consistent during long-term treatment, while untreated individuals had consistently higher levels.(27)

Improved feeding abilities

People who received fosdenopterin were more likely to eat food orally (by mouth), and they took longer time to require tube feeding compared to untreated individuals. Treated patients were 7.8 times more likely to eat orally at their last check-up than untreated patients. The time before needing tube feeding was significantly longer for treated patients compared to untreated controls.(27)

Fosdenopterin improves the growth of patients with MoCD Type A

Treated patients showed better growth compared to untreated individuals. At the last check-up, treated patients were more likely to have growth close to or above average compared to untreated individuals**.**(27)

Fosdenopterin improves the development of patients with MoCD Type A

Treated patients showed improved motor function (ability of the body to move and perform different tasks) compared to untreated controls. Cognitive assessments (how well a person's brain is working in terms of thinking, understanding, and remembering) showed that fosdenopterin-treated patients generally performed better, with some staying consistent, and others improving in their abilities.(27)

Participants who received treatment were more likely to sit without assistance after 12 months compared to those who did not get treated. Both groups had individuals experiencing seizures, but in the fosdenopterin-treated group, there was a better rate of resolving or controlling seizures.(27)

The neuroimaging (taking pictures of the brain to see the condition) results showed that both groups had abnormalities, but when doctors checked more directly through examinations, they found that the patients who received fosdenopterin had better outcomes.(27)

Additionally, patients showed fewer issues with muscle tension and reflexes, suggesting a positive impact of the fosdenopterin treatment on the health of their brain.(27)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Because of the young age of the patients, quality of life data were not collected in the studies, as this often involves an individual having to describe pain and other issues, which may be difficult for younger individuals to express accurately. Therefore, alternative methods, such as the gross motor function scoring, were used to understand changes in overall wellbeing, which can be used to assume changes to quality of life. If a person can improve their ability to move, eat and think due to the medication, they are less likely to be relying on other people to help them in day-to-day life, less prone to accidents, and are more capable of attending social events, the workplace, and recreational activities. This should result in an improvement of their overall health, both mental and physical, and as a result, quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, fosdenopterin can cause side effects. The most common (i.e., affecting more than 1 in 10 people) are problems related to the catheter, which can include pain, discharge, redness, or inflammation. Catheter-related reactions should be managed according to the doctor’s instructions.

Animal studies have identified that fosdenopterin can cause a condition in which the skin or eyes become very sensitive to sunlight or other forms of light, called phototoxicity. Therefore, fosdenopterin-treated patients or their caregivers are advised to avoid or minimise patient exposure to direct sunlight and artificial ultraviolet (UV) light exposure (i.e., UVA or UVB phototherapy) and adopt precautionary measures (e.g., have the patient wear protective clothing and hats,

use broad spectrum sunscreen with high sun protection factor (SPF) in patients 6 months of age and older, and wear sunglasses when exposed to the sun). If photosensitivity occurs, advise caregivers/patients to seek medical attention immediately and consider a dermatological evaluation.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

> Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments. Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Fosdenopterin is a life-saving and life-changing treatment for patients with MoCD Type A, who are currently offered no treatment choices. Fosdenopterin is novel because it is the only treatment that is disease-modifying for this illness. Traditional treatments focus on treating symptoms, but fosdenopterin treats the root cause and can change the course of the disease.

It also has a manageable safety profile, which is an important thing to consider when a doctor is deciding treatment options. Once a caregiver has received training, the process is relatively straight forward and intravenous administration generally takes about 3.5 minutes for a 10kg child and 10 minutes for a 30 kg child. This ensures that the treatment will not place too much of a time constraint on the patient or caregiver. Treating with fosdenopterin should take away the need for current medications and feeding through a feeding tube, making treatment easier for both patients and their caregivers.

In addition to its effects on health, fosdenopterin has a large impact on the lives of patients and the people who care for them. Fosdenopterin not only gives patients hope by providing the missing substance, cPMP, and having a unique disease-modifying effect, but also improves the daily lives of those who are affected, by making the disease and its symptoms easier to manage.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

> Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
> What is the impact of any disadvantages highlighted compared with current treatments

Treatment with fosdenopterin has no disadvantages compared to current treatments, as current treatments are purely supportive, and are not designed to treat the root cause of the disease.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

> The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
> If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
> How the condition, taking the new treatment compared with current treatments affects your quality of life.

It is proposed that fosdenopterin be used alongside the current symptom-controlling treatments offered through the NHS. Data from the trials for fosdenopterin support the idea that patients receiving fosdenopterin had much improved outcomes compared to the natural history cohort.(27) Treatment improves important health outcomes, such as increasing survival rates and positively impacting feeding abilities, growth parameters, and developmental assessments.(27) These outcomes are directly relevant to addressing the pressing needs and challenges faced by patients dealing with MoCD Type A.

Fosdenopterin treatment may have positive financial implications for patients and their families. The observed improvements in health outcomes, such as increased survival rates and improved development,(27) could potentially lead to reduced long-term healthcare costs associated with managing MoCD Type A. Because the treatment can be administered at home, there may be fewer hospital visits required which can certainly benefit families financially.

The improvements in outcomes suggest an improvement in the overall quality of life for individuals with MoCD Type A through fosdenopterin. Positive outcomes in survival rates, feeding abilities, growth, and developmental assessments collectively contribute to an enhanced quality of life.(27)

To assess the impact of fosdenopterin in terms of costs compared to benefits, the company conducted a health economic analysis to calculate whether the drug provides good value for money, i.e., 'cost-effectiveness'.

The analysis compares the cost-effectiveness of fosdenopterin with standard of care (SoC). Fosdenopterin is shown to extend patients' lives significantly, with an expected gain of 18.31 quality-adjusted life years (QALYs; a way of measuring how much a treatment not only prolongs life but also improves its quality) compared to SoC. However, it comes at an extra cost, resulting in an incremental cost-effectiveness ratio, i.e., the extra money spent for each extra bit of health improvement with the new treatment, of £1,971,011 at full price.

Analysis to assess uncertainty revealed that the main factors affecting the model are structural parameters (such as the discount rate) and specific population criteria (early-onset MoCD Type A) and considerations for caregivers.

Strengths of the study include the use of detailed patient-level data to inform long-term survival, baseline characteristics, adverse events, healthcare resource use, and medication use. However, there are challenges due to the rarity of the condition, such as limited data on patient numbers, long-term efficacy, quality of life in MoCD Type A, and complete healthcare resource use.

To address these gaps, the study used approaches like selecting a similar condition (Dravet syndrome) as a proxy to characterise the disease, confirmed by a clinical expert.(28) Assumptions were validated by experts, including the impact of treatment on quality of life (QoL) and long-term survival.(29)

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Fosdenopterin is an innovative medicine that has been given 'Orphan' status by the EMA and FDA (the regulatory body within the United States), because the drug is intended to treat a rare, life-threatening and long-term disease (22).

Currently, there are no effective approved treatments for MoCD Type A in England. Current treatments are supportive, which means that they do not target the disease, only the symptoms, and therefore the patient state will continue to worsen.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Due to the rarity of the condition, it is unlikely that there are any equality issues associated with certain groups with the condition.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

- https://www.nulibry.com/
- https://clinicaltrials.gov/ct2/show/NCT01640717
- https://clinicaltrials.gov/ct2/show/NCT02047461
- https://www.ema.europa.eu/en/medicines/human/EPAR/nulibry

Further information on NICE and the role of patients:

Public Involvement at NICE
NICE's guides and templates for patient involvement in HTAs
EFPIA – Working together with patient groups (PDF)
National Health Council Value Initiative

4b) Glossary of terms

Awareness: The state of being conscious of and responsive to one's surroundings.

Caregiver: A person responsible for providing care and support, often for someone who is unable to care for themselves.

Catheter: A catheter is a thin, flexible tube that doctors use to help with different medical issues. It can be put into your body to drain fluids, give medicines, or measure certain things. It's a tool that doctors use to help with treatments and procedures when needed.

Central venous line: A line in a large vein near the heart.

European Medicines Agency: The regulatory body that ensures the safety, effectiveness, and quality of drugs before they can be sold and used in EU countries.

Fosdenopterin: A replacement therapy for MoCD Type A, providing an external source of cPMP to restore the body's ability to make MoCo and reduce elevated sulphite and s-sulphocysteine (SSC) levels.

Gene: The basic unit of heredity, carrying information that determines the traits and characteristics of living organisms.

Inborn error of metabolism: A genetic disorder affecting the body's ability to carry out specific chemical reactions related to the processing of nutrients or waste products.

Metabolism: The set of chemical processes within living organisms to maintain life, including the breakdown of substances to produce energy.

Mild: The severity level indicating a low degree of impact or harm.

***MOCS1* gene:** The specific gene associated with MoCD Type A, leading to the inability to produce cPMP.

Muscle weakness: Lack of strength in the muscles, leading to difficulties in movement and coordination.

Phototoxicity: Adverse skin reactions induced by exposure to light.

Seizures: Sudden, uncontrolled electrical disturbances in the brain, resulting in abnormal behaviour, movements, or sensations.

Sepsis: A severe infection that can lead to systemic inflammation and organ failure.

Skin disorders: Adverse conditions affecting the skin and subcutaneous tissues.

Startle reactions: Sudden, involuntary responses to unexpected stimuli, characterised by a quick and exaggerated movement or reaction.

Sulphites: Compounds formed in the body that cannot be broken down in individuals with MoCD Type A, leading to toxicity, particularly harmful to the brain.

Symptoms: Observable signs or indications of a medical condition, such as difficulty feeding, seizures, decreased awareness, increased startle reactions, and weak or stiff muscles in the context of MoCD Type A.

Toxicity: The degree to which a substance can cause harm to an organism or system.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID6264 fosdenopterin clarification questions EAG [CON]	**V3**	**Yes**	**13/05/2024**

Section A: Clarification on effectiveness data

A1. Please can the company clarify what is meant by 'integrated efficacy results'? Does this involve pooling the individual patients from each fosdenopterin trial into one dataset? Please justify the approach taken.

Yes, the integrated efficacy results (analysis) represent the pooled analysis from each of the fosdenopterin clinical trials, specifically studies MCD-201, MCD-202, and MCD-501, along with a comparison to natural history data from untreated patients in study MCD-502. This integration aimed to summarise the clinical efficacy data for cyclic pyranopterin monophosphate (cPMP), across these studies. The objective was to provide a robust analysis that allows for an interpretation of the response to cPMP in the target population and to compare this response to the natural progression of the disease in comparable patients who participated in the natural history study.

The approach involved pooling data to overcome the limitations associated with the small population size inherent in studying an often-fatal ultra-rare disease, the heterogeneity of disease presentation, and the mix of retrospective and prospective data collection for both treated and untreated (natural history control) patients. This methodology was necessary as it allows for a more comprehensive assessment of fosdenopterin's efficacy by making use of the totality of evidence available across multiple studies, thereby enhancing the statistical power and reliability of the efficacy conclusions.

A2. Please clarify the approach taken to propensity score matching in the integrated efficacy results and confirm whether the same approach was taken in the results presented in the clinical section and in the model.

The approach to data integration and analysis across studies for fosdenopterin is provided in the Integrated Summary of Efficacy Statistical Analysis Plan (ISE SAP), which the company will provide as an Appendix.

The integrated efficacy data encompasses various variables, including patient disposition, demographics, molybdenum cofactor deficiency (MoCD) family history, drug exposure, and a range of efficacy endpoints such as overall survival, biomarkers, and neurologic examinations.

The analysis delineates three primary populations:

- Full Analysis Set (FAS): Includes all MoCD Type A patients, both treated and untreated.
- Prospective Full Analysis Set (PFAS): Constitutes a subset of the FAS, including patients followed prospectively.
- Genotype-Matched Analysis Set (GMAS): Comprises patients included in the m:n (where m is the number of treated patients and n is the number of natural history controls in a given match) matching based on genotype, ensuring a rigorous comparison between treated patients and natural history controls.

Subgroups within these populations were identified to examine differences in efficacy based on factors such as treatment initiation timing, gender, and symptom onset. The model also explores a subset of patients excluding those with late onset disease (n=4), labelled as 'Early onset patients' in the model).

To ensure comparability between treated patients and natural history controls, a matching algorithm was applied. Treated patients were matched with one or multiple controls from the natural history study based on genotype. The following approach was utilised to determine matching:

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

The protein products of *MOCS1, MOCS1A,* and *MOCS1B* contain sites and regions with highly conserved amino acids across all cellular life, from single-celled bacteria

to humans. Only a small group of proteins are currently known to have this high level of conservation, with nearly all being intimately connected to the sustaining of life. In discussions with researchers who provided much of the published data on protein structure, the sponsor matched treated patients to natural history control patients based on the known impact of the mutations on either *MOCS1A* or *MOCS1B*. Details on the matching criteria used for patients who were not an exact genotype match are provided in Comparative Case Reports.

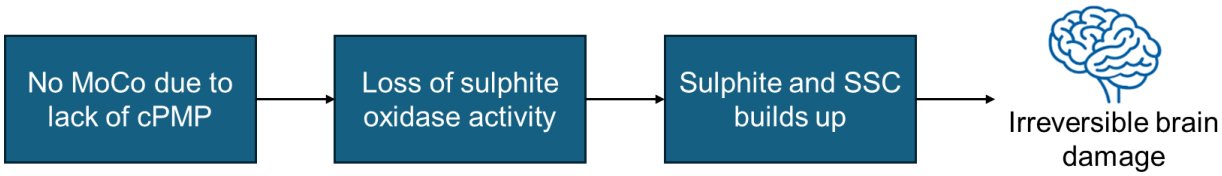
The matching criteria utilising genotype that was conducted is appropriate and informs on the efficacy of fosdenopterin. This is based on the fact that key baseline characteristics of the patients are comparable, thus supporting the matching algorithm across treated and untreated patients as outlined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

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

A3. Please can the company provide details of fosdenopterin's mechanism of action in lay terms?

MoCD Type A results from an error in the gene called *MOCS1*. This interferes with the body making an essential substance called cyclic pyranopterin monophosphate (cPMP), which leads to a lack of molybdenum cofactor (MoCo) .(1) When this substance is missing, certain compounds (sulphites) that are formed in the body, cannot be broken down (2, 3). These compounds are toxic to the brain and can negatively affect or delay the development of a child. (4-7) Please see Figure 1 to see this pathway.

Figure 1: MoCD Type A disease pathway



Abbreviations: cPMP, cyclic pyranopterin monophosphate; MoCo, molybdenum cofactor.

Fosdenopterin provides the missing substance, cPMP, that the body needs to break down the harmful sulphite compounds associated with MoCD Type A.(8) Fosdenopterin is novel because the current standard of care is used to treat the symptoms, rather than the cause of the disease.(8)

A4. Please justify the assumptions taken with regard to health-related quality of life in the submission. If we understand correctly, no information on quality of life was collected in any of the clinical studies, no mapping was conducted and no utilities were identified in the literature relating to the target population. Utilities from Dravet syndrome were used as a proxy. Please provide any published evidence or clinical expert opinion about how similar the quality of life impact of these two conditions is likely to be.

Due to the extreme rarity of MoCD Type A and consequent scarcity of literature, particularly regarding health-related quality of life (HRQoL), it was necessary to seek an alternative condition that could serve as a proxy for the purpose of assessing HRQoL impact. Dravet syndrome (DS) was selected as a suitable proxy based on several factors.

- Similarities in disease characteristics: Both MoCD and DS are rare and severe neurological disorders with onset in early childhood, characterised by frequent and severe seizures, developmental delays, and cognitive impairments. This clinical resemblance in terms of the burden of disease and impact on daily functioning suggests that the implications for quality of life have the potential to be similar, even though the aetiologies differ. DS, notably one of the most severe forms of epileptic encephalopathy, shares the lifelong condition status with MoCD, including a significant early mortality rate and a likelihood of persistent seizures despite treatment. Such parallels provide a basis for assuming comparable HRQoL detriments in both conditions. (4, 9)

- Furthermore, DS has a relatively more substantial body of research available, including data on quality of life and health state utilities, which are not available for MoCD. Given that DS is also a developmental and genetic epileptic encephalopathy with seizures beginning in infancy and associated impairments in motor control, behaviour, and cognition, it provides a framework from which to draw parallels.(4, 9)

To ensure transparency and robustness, the company conducted a systematic literature review (SLR) to identify health-related quality of life (HRQoL) data and health state utility (HSU) values for MoCD Type A (Appendix H). However, the review identified no studies with HSU values specifically for MoCD Type A. Therefore, the company conducted a further SLR for a similar disease, DS, to obtain HSU values that could inform the economic model. The company sought to strengthen the model's assumptions by engaging with a clinical expert, a paediatric neurologist experienced in the management of MoCD Type A. This expert, through a clinical validation exercise, confirmed the suitability of using HRQoL data from DS as a proxy for MoCD Type A. Please see Appendix M of the company submission for more information.

A5. There is inconsistency in the number of cPMP treated patients throughout the submission for example:

- **Table 12 reports 4, 8 and 3 patients in MCD-501, -201 and -202, respectively with a total of 15 patients**

- **Table 13 reports the same patient numbers in each trial but a total of 14 patients**

- **Tables 18, 21 and 22 report MCD-202 having 2 patients rather than 3 with a total of 14 patients**

Please can the company clarify the sample size for patients receiving cPMP, amend the tables that are inconsistent or, if appropriate, justify differing patient numbers between tables?

Table 12 accurately reports 4, 8, and 3 patients in the MCD-501, MCD-201, and MCD-202 trials, respectively, totalling 15 patients, at the October 2021 data cut-off point.

The inconsistency in Table 13, which mirrors the patient counts per trial but totals 14, is due to a typographical error; the correct total is indeed 15.

The variances noted in Tables 18, 21, and 22, where MCD-202 is shown to have 2 patients instead of 3, leading to a total of 14 patients, are explained by the data cut-off dates. Tables 12 and 13 include data up to October 2021, capturing the enrolment of an additional patient in the MCD-202 trial, whereas Tables 18, 21, and 22 utilise a cut-off of October 2020, missing this later enrolment.

Section B: Clarification on cost-effectiveness data

Literature searches.

B1 Please could the company confirm which search filter was used to identify cost effectiveness studies in Appendix G?

The following search terms were used to filter for MoCD cost-effectiveness studies in Embase:

exp pharmacoeconomics/
exp "economics, nursing"/
Pharmacoeconomic$.af.
health economic$.mp.
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp.

Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost of illness.mp.
cost-benefit analysis/
(cost-effectiveness or cost-utility).af.
exp costs/ and "cost analysis"/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
Drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
exp "Health Services"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$ or us$)).mp.
exp hospitalization/ or hospitalisation.af. or hospitalization.af.
exp caregivers/ or caregivers.af
(carer or carers).af.

The following search terms were used to filter for MoCD cost-effectiveness studies in MEDLINE:

exp pharmacoeconomics/
exp economics, nursing/
Pharmacoeconomic$.af.
health economic$.mp.
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp.
Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost of illness.mp.
cost-benefit analysis/
(cost-effectiveness or cost-utility).af.
exp costs/ and cost analysis/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
Drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.

simulation.mp.
exp Health Care Costs/
exp health resources/
exp Hospital Costs/
exp Resource Allocation/
exp Health Services/
((health care or resourc$ or service$ or hospital$) adj2 (utili$ or cost$ or us$)).mp.
exp hospitalization/ or hospitalisation.af. or hospitalization.af.
exp caregivers/ or caregivers.af.
(carer or carers).af.

The following search terms were used to filter for MoCD cost-effectiveness studies in Cochrane Library:

pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
economic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(fee? and charge?).mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw]
budget?.mp.
Direct service cost?.mp.
Drug cost?.mp.
Health expenditure?.mp.
expenditure?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(monte and carlo).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
microsimulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]

patient level simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
discrete event simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]

The following search terms were used to filter for MoCD cost-effectiveness studies in Econlit:

pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=heading words, abstract, title, country as subject]
economic?.mp. [mp=heading words, abstract, title, country as subject]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=heading words, abstract, title, country as subject]
(fee? and charge?).mp. [mp=heading words, abstract, title, country as subject]
budget?.mp.
Drug cost?.mp.
Health expenditure?.mp.
budget?.mp. [mp=heading words, abstract, title, country as subject]
expenditure?.mp. [mp=heading words, abstract, title, country as subject]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=heading words, abstract, title, country as subject]
(monte and carlo).mp. [mp=heading words, abstract, title, country as subject]
microsimulation.mp. [mp=heading words, abstract, title, country as subject]
patient level simulation.mp. [mp=heading words, abstract, title, country as subject]

discrete event simulation.mp. [mp=heading words, abstract, title, country as subject]
simulation.mp. [mp=heading words, abstract, title, country as subject]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=heading words, abstract, title, country as subject]

The following search terms were used to filter for DS cost-effectiveness studies in Embase:

exp pharmacoeconomics/
exp economics, nursing/
exp Quality Adjusted Life Year$/
exp QALY/
(Incremental Cost Effectiveness Ratio or ICER).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Pharmacoeconomic$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
health economic$/
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost-benefit analysis/
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
exp costs/ and "cost analysis"/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
drug costs/
Health expenditures/

budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$)).mp.
exp caregivers/ or caregivers.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Carer$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]

The following search terms were used to filter for DS cost-effectiveness studies in MEDLINE:

exp pharmacoeconomics/
exp economics, nursing/
exp Quality Adjusted Life Year$/
exp QALY/
(Incremental Cost Effectiveness Ratio or ICER).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Pharmacoeconomic$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
health economic$/
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Cost allocation/
Cost control/

Cost savings/
Cost of Illness/
cost-benefit analysis/
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
exp costs/ and "cost analysis"/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$)).mp.
exp caregivers/ or caregivers.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Carer$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]

The following search terms were used to filter for DS cost-effectiveness studies in Cochrane Library:

pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
economic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(fee? and charge?).mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw]
budget?.mp.
Direct service cost?.mp.
Drug cost?.mp.
Health expenditure?.mp.
expenditure?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(monte and carlo).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
microsimulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
patient level simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
discrete event simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]

The following search terms were used to filter for MoCD cost-effectiveness studies in Econlit:

exp pharmacoeconomics/
exp economics, nursing/
exp Quality Adjusted Life Year$/
exp QALY/
(Incremental Cost Effectiveness Ratio or ICER).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
Pharmacoeconomic$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
health economic$/
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost-benefit analysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
(cost-effectiveness or cost-utility).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
exp costs/ and "cost analysis"/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/

(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$)).mp.
exp caregivers/ or caregivers.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
Carer$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

No additional filters were used in any of the searches.

B2 Please could the company confirm which search filter was used to identify quality of life studies in Appendix H?

The following search terms were used to filter for quality of life studies in Embase:

("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").ti,ab.
(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").ti,ab.
("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).ti,ab.
("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D" or "SF 36").ti,ab.
(15D or 16D or 17D).ti,ab.
("standard gamble" or SG).ti,ab.
("time trade off" or "time trade-off" or "time tradeoff" or TTO).ti,ab.
("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").ti,ab.
disutilit$.ti,ab.
(health adj1 stat*).ti,ab. or exp Health Status/
(utility adj1 (value* or weight*)).ti,ab.

exp statistical model/
preference$.ti,ab.
*patient preference/
(utilit* or "health utility index" or "utilities index").ti,ab.
(map$ or mapping or regression or "cross walking" or "cross-walking").ti,ab.
("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").ti,ab.
quality of life index.ti,ab. or exp "quality of life index"/
quality adjusted life year.ti,ab. or exp quality adjusted life year/
(qaly or daly or "adjusted life").ti,ab.
("quality adjusted" or "disability adjusted").ti,ab.
disability.ti,ab. or exp disability/
disabled person.ti,ab. or exp disabled person/
life expectancy.ti,ab. or exp life expectancy/
(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").ti,ab.
quality of life.ti,ab. or exp "quality of life"/
(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).ti,ab.
(Health utilities index or HUI).ti,ab.
(time trade off or time trade-off or ("TTO" adj2 "time trade")).ti,ab.
(short form 6D or short-form 6D).ti,ab.
(standard gamble or ("SG" adj2 "standard gamble")).ti,ab.
(15D or 16D or 17D).ti,ab.
exp short form 12/ or exp short form 20/ or exp short form 36/
("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").ti,ab.
(medical outcome adj1 (survey or stud*)).ti,ab.
(QoL or HRQoL or HRQL).ti,ab.
exp "quality of life"/
(health related quality of life or health-related quality of life).ti,ab.
((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).ti,ab.
health state$.ti,ab.
utilit*.ti,ab.
Patient Preference/ or preference.ti,ab.
(map$ or regression).ti,ab.
exp health status/
health survey/
exp daily life activity/
("Activities of Daily Living" or "IADL").ti,ab.
Psychometrics.ti,ab. or exp psychometry/
("health year equivalent" or "HYE").ti,ab.

The following search terms were used to filter for quality of life studies in MEDLINE:

(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.
(Health utilities index or HUI).mp.
(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.
(short form 6D or short-form 6D).mp
(standard gamble or ("SG" adj2 "standard gamble")).mp.
(15D or 16D or 17D).mp.
(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp.
(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp.
(medical outcomes survey or MOS).mp.
(Quality of wellbeing index or QWB).mp.
(QoL or HRQoL or HRQL).mp.
quality of life.mp. or exp "Quality of Life"/
(health related quality of life or health-related quality of life).mp.
((quality of life or QoL) adj10 (question$ or instrument or scale$1 or score$1)).mp.
health state$.mp.
utilit$.mp.
Patient Preference/ or preference.mp.
(map$ or regression).mp.
health status.mp. or *Health Status/
health status indicators.mp. or *Health Status Indicators/
*"Activities of Daily Living"/
Health Surveys/ or health survey.mp.
Psychometrics/ or psychometric.mp.
(health* year* equivalent* or HYE*).mp.
("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.
(AQOL or "Assessment of Quality of Life").mp.
("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.
("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.
("15D" or "16D" or "17D").mp.
("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.
"standard gamble".mp.
("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.
disutilit$.mp.
(health adj1 stat*).mp. or exp Health Status/

exp Models, Economic/
(utility adj (value* or weight*)).mp.
preference$.mp.
exp Patient Preference/
(utilit* or "health utility index" or "utilities index").mp.
(map$ or mapping or regression or "cross walking" or "cross-walking").mp.
("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.
quality of life index.mp.
quality adjusted life year.mp. or exp Quality-Adjusted Life Years/
("qaly" or "daly" or "adjusted life").mp.
("quality adjusted" or "disability adjusted").mp.
exp Disability Evaluation/ or disability.mp.
disabled person.mp. or exp Disabled Persons/
life expectancy.mp. or exp Life Expectancy/
("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.
quality of life.mp. or exp "quality of life"/

The following search terms were used to filter for cost-effectiveness studies in Cochrane Library:

(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.
(Health utilities index or HUI).mp.
(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.
(short form 6D or short-form 6D).mp.
(standard gamble or ("SG" adj2 "standard gamble")).mp.
(15D or 16D or 17D).mp.
(short form 36 or shortform 36 or SF-36 or SF36 or SF 36).mp.
(short form 12 or shortform 12 or SF12 or SF-12 or SF 12).mp.
(medical outcomes survey or MOS).mp.
(Quality of wellbeing index or QWB).mp.
(QoL or HRQoL or HRQL).mp.
quality of life.mp. or exp "Quality of Life"/
(health related quality of life or health-related quality of life).mp.
((quality of life or QoL) adj10 (question$ or instrument or scale$1 or score$1)).mp.
health state$.mp.

utilit$.mp.
Patient Preference/ or preference.mp.
(map$ or regression).mp.
health status.mp. or *Health Status/
health status indicators.mp. or *Health Status Indicators/
*"Activities of Daily Living"/
Health Surveys/ or health survey.mp.
Psychometrics/ or psychometric.mp.
(health* year* equivalent* or HYE*).mp.
("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.
(AQOL or "Assessment of Quality of Life").mp.
("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.
("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.
("15D" or "16D" or "17D").mp.
("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.
"standard gamble".mp.
("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.
disutilit$.mp.
(health adj1 stat*).mp. or exp Health Status/
exp Models, Economic/
(utility adj (value* or weight*)).mp.
preference$.mp.
exp Patient Preference/
(utilit* or "health utility index" or "utilities index").mp.
(map$ or mapping or regression or "cross walking" or "cross-walking").mp.
("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.
quality of life index.mp.
quality adjusted life year.mp. or exp Quality-Adjusted Life Years/
("qaly" or "daly" or "adjusted life").mp.
("quality adjusted" or "disability adjusted").mp.
exp Disability Evaluation/ or disability.mp.
disabled person.mp. or exp Disabled Persons/

life expectancy.mp. or exp Life Expectancy/
("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.
quality of life.mp. or exp "quality of life"/

No additional filters were used in any of the searches.

B3 Please could the company supply the literature searches and methods used for the costs SLR (referenced as Appendix I but we cannot see this document in the CS)? Could the company please supply any missing appendices. It would be appreciated if these could be supplied before the other answers.

'Appendix I' should have referred to Appendix G, this was a typographical error.

The following search terms were used to filter for MoCD costs in the EMBASE library.

((molybdenum and cofactor and deficiency) or "'Molybdenum cofactor deficiency'" or (molybdoflavoprotein and (enzyme or enzymes) and deficiency) or MOCD or MOCOD or (MOCO and deficiency) or (("'sulfite oxidase'" or "'sulphite oxidase'") and ("'xanthine oxidase'" or "'xanthine dehydrogenase'") and "'aldehyde oxidase'" and deficiency)).mp.
exp pharmacoeconomics/
exp "economics, nursing"/
Pharmacoeconomic$.af.
health economic$.mp.
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp.
Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost of illness.mp.
cost-benefit analysis/
(cost-effectiveness or cost-utility).af.
exp costs/ and "cost analysis"/
exp "fees and charges"/

exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
Drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
exp "Health Services"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$ or us$)).mp.
exp hospitalization/ or hospitalisation.af. or hospitalization.af.
exp caregivers/ or caregivers.af
(carer or carers).af.
2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
1 and 45

The following search terms were used to filter for MoCD costs in the MEDLINE library.

((molybdenum and cofactor and deficiency) or "Molybdenum cofactor deficiency" or (molybdoflavoprotein and (enzyme or enzymes) and deficiency) or MOCD or MOCOD or (MOCO and deficiency) or (("sulfite oxidase" or "sulphite oxidase") and ("xanthine oxidase" or "xanthine dehydrogenase") and "aldehyde oxidase" and deficiency)).af.
exp pharmacoeconomics/
exp economics, nursing/
Pharmacoeconomic$.af.
health economic$.mp.
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp.
Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost of illness.mp.
cost-benefit analysis/
(cost-effectiveness or cost-utility).af.
exp costs/ and cost analysis/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
Drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.

(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp Health Care Costs/
exp health resources/
exp Hospital Costs/
exp Resource Allocation/
exp Health Services/
((health care or resourc$ or service$ or hospital$) adj2 (utili$ or cost$ or us$)).mp.
exp hospitalization/ or hospitalisation.af. or hospitalization.af.
exp caregivers/ or caregivers.af.
(carer or carers).af.
or/2-44
1 and 45

The following search terms were used to filter for MoCD costs in the Cochrane library.

((molybdenum and cofactor and deficiency) or "Molybdenum cofactor deficiency:kw" or (molybdoflavoprotein and (enzyme or enzymes) and deficiency) or MOCD or MOCOD or (MOCO and deficiency) or (("sulfite oxidase" or "sulphite oxidase") and ("xanthine oxidase" or "xanthine dehydrogenase") and "aldehyde oxidase" and deficiency)).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
economic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(fee? and charge?).mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw]
budget?.mp.
Direct service cost?.mp.

Drug cost?.mp.
Health expenditure?.mp.
expenditure?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(monte and carlo).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
microsimulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
patient level simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
discrete event simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
or/2-33
1 and 34

The following search terms were used to filter for MoCD costs in the Econlit library.

(molybdenum cofactor deficiency or MoCD or sulfite oxidase deficiency or sul$ite oxidase deficiency or MOCS1 gene mutation).mp. [mp=heading words, abstract, title, country as subject]
pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=heading words, abstract, title, country as subject]
economic?.mp. [mp=heading words, abstract, title, country as subject]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=heading words, abstract, title, country as subject]
(fee? and charge?).mp. [mp=heading words, abstract, title, country as subject]
budget?.mp.
Drug cost?.mp.

Health expenditure?.mp.
budget?.mp. [mp=heading words, abstract, title, country as subject]
expenditure?.mp. [mp=heading words, abstract, title, country as subject]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=heading words, abstract, title, country as subject]
(monte and carlo).mp. [mp=heading words, abstract, title, country as subject]
microsimulation.mp. [mp=heading words, abstract, title, country as subject]
patient level simulation.mp. [mp=heading words, abstract, title, country as subject]
discrete event simulation.mp. [mp=heading words, abstract, title, country as subject]
simulation.mp. [mp=heading words, abstract, title, country as subject]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=heading words, abstract, title, country as subject]
or/2-33
1 and 34

The following search terms were used to filter for DS costs in the EMBASE library.

((Dravet and syndrome) or 'Dravet syndrome' or (severe and myoclonic and epilepsy and infancy) or 'severe myoclonic epilepsy in infancy' or 'severe myoclonic epilepsy of infancy' or SMEI or (epilepsy and polymorphic and seizures) or 'epilepsy with polymorphic seizures' or (polymorphic and epilepsy and infancy) or 'polymorphic epilepsy in infancy' or 'polymorphic epilepsy of infancy' or PMEI or SMEB).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
exp pharmacoeconomics/
exp economics, nursing/
exp Quality Adjusted Life Year$/
exp QALY/
(Incremental Cost Effectiveness Ratio or ICER).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Pharmacoeconomic$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
health economic$/
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Cost allocation/
Cost control/
Cost savings/

Cost of Illness/
cost-benefit analysis/
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
exp costs/ and "cost analysis"/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$)).mp.
exp caregivers/ or caregivers.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Carer$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
or/2-44
1 and 45

The following search terms were used to filter for DS costs in the MEDLINE library.

((Dravet and syndrome) or 'Dravet syndrome' or (severe and myoclonic and epilepsy and infancy) or 'severe myoclonic epilepsy in infancy' or 'severe myoclonic epilepsy of infancy' or SMEI or (epilepsy and polymorphic and seizures) or 'epilepsy with polymorphic seizures' or (polymorphic and epilepsy and infancy) or 'polymorphic epilepsy in infancy' or 'polymorphic epilepsy of infancy' or PMEI or SMEB).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
exp pharmacoeconomics/
exp economics, nursing/
exp Quality Adjusted Life Year$/

exp QALY/
(Incremental Cost Effectiveness Ratio or ICER).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Pharmacoeconomic$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
health economic$/
(economic$ and (aspect$ or evaluat$ or analys$ or model$)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Cost allocation/
Cost control/
Cost savings/
Cost of Illness/
cost-benefit analysis/
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
exp costs/ and "cost analysis"/
exp "fees and charges"/
exp budgets/
(cost$ adj2 (unit$ or utili$ or analys$ or estimate$ or effect$ or benefit$ or minimi$ or stud$ or effic$)).mp.
Direct service costs/
direct cost$.mp.
drug costs/
Health expenditures/
budget$.mp.
expenditure$.mp.
models, economic/
markov chains/
monte carlo method/
decision tree/
(decision adj2 (tree$ or analys$ or model$)).mp.
markov$.mp.
(monte adj carlo).mp.
(cba or cea or cua or cma or cca).mp.
microsimulation.mp.
patient level simulation.mp.
discrete event simulation.mp.
simulation.mp.
exp "Health Care Costs"/
exp "health resources"/
exp "Hospital Costs"/
exp "Resource Allocation"/
(("health care" or resourc$ or service$ or hospital$) adj2 (utili$ or cost$)).mp.
exp caregivers/ or caregivers.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
Carer$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
or/2-44

1 and 45

The following search terms were used to filter for DS costs in the Cochrane library.

((Dravet and syndrome) or 'Dravet syndrome' or (severe and myoclonic and epilepsy and infancy) or 'severe myoclonic epilepsy in infancy' or 'severe myoclonic epilepsy of infancy' or SMEI or (epilepsy and polymorphic and seizures) or 'epilepsy with polymorphic seizures' or (polymorphic and epilepsy and infancy) or 'polymorphic epilepsy in infancy' or 'polymorphic epilepsy of infancy' or PMEI or SMEB).mp. [mp=heading words, abstract, title, country as subject]
pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
economic?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(fee? and charge?).mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw]
budget?.mp.
Direct service cost?.mp.
Drug cost?.mp.
Health expenditure?.mp.
expenditure?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
(monte and carlo).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
microsimulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
patient level simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
discrete event simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
simulation.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw]
or/2-33
1 and 34

The following search terms were used to filter for DS costs in the Econlit library.

((Dravet and syndrome) or 'Dravet syndrome' or (severe and myoclonic and epilepsy and infancy) or 'severe myoclonic epilepsy in infancy' or 'severe myoclonic epilepsy of infancy' or SMEI or (epilepsy and polymorphic and seizures) or 'epilepsy with polymorphic seizures' or (polymorphic and epilepsy and infancy) or 'polymorphic epilepsy in infancy' or 'polymorphic epilepsy of infancy' or PMEI or SMEB).mp. [mp=heading words, abstract, title, country as subject]
pharmacoeconomics.mp.
(economic? and nursing).mp.
Pharmacoeconomic?.mp. [mp=heading words, abstract, title, country as subject]
economic?.mp. [mp=heading words, abstract, title, country as subject]
Cost allocation.mp.
Cost control.mp.
Cost savings.mp.
Cost of Illness.mp.
cost-benefit analysis.mp.
(cost-effectiveness or cost-utility).mp. [mp=heading words, abstract, title, country as subject]
(fee? and charge?).mp. [mp=heading words, abstract, title, country as subject]
budget?.mp.
Drug cost?.mp.
Health expenditure?.mp.
budget?.mp. [mp=heading words, abstract, title, country as subject]
expenditure?.mp. [mp=heading words, abstract, title, country as subject]
(model? and economic).mp.
(markov and chain).mp.
monte carlo method.mp.
decision tree.mp.
markov?.mp. [mp=heading words, abstract, title, country as subject]
(monte and carlo).mp. [mp=heading words, abstract, title, country as subject]
microsimulation.mp. [mp=heading words, abstract, title, country as subject]
patient level simulation.mp. [mp=heading words, abstract, title, country as subject]
discrete event simulation.mp. [mp=heading words, abstract, title, country as subject]
simulation.mp. [mp=heading words, abstract, title, country as subject]
Health Care Cost?.mp.
(health and resource?).mp.
(Hospital and Cost?).mp.
Resource Allocation.mp.
(Health and Service?).mp.
(carer or carers).mp. [mp=heading words, abstract, title, country as subject]
or/2-33
1 and 34

Interpretation of the model inputs and results

B4. PRIORITY.

[redacted]?[redacted]

[redacted]

B5. PRIORITY. Acknowledging the paucity of data to quantify the natural history of MoCD Type A (CS Section B.3.2.3), please can the company clearly describe how its model captures the following expected benefits of treatment with fosdenopterin, both in terms of costs and/or QALYs:

- **Improved patient survival**
- **Stabilisation in the incidence of seizures**
- **Reduced need for nasogastric feeding**
- **No worsening in mobility**

In responding to the request above, please can the company signpost where the relevant supporting evidence for these features of the model is reported within the CS and/or published literature?

The model captures the following range of benefits for patients treated with fosdenopterin for MoCD Type A:

- "Improved patient survival" is captured using the Kaplan-Meier data for standard of care (SoC) and fosdenopterin-treated patients. Kaplan-Meier data and their extrapolations are provided on the 'Survival curves' sheet of the model and are taken from derived from studies MCD-201, MCD-202 and MCD-501 for the fosdenopterin arm, and MCD-502 for the SoC arm. Survival benefit is captured in the incremental LYs gained by patients in the fosdenopterin arm vs SoC. The choice of extrapolation for the fosdenopterin arm was supported by visual inspection with a clinical expert (Appendix M). High mortality for untreated MoCD Type A is described in Section B.1.4.4 and the literature.(6, 7) Further rationale is provided in B.3.3.2. Increased survival

has an impact on incremental costs as patients living longer will incur healthcare resource use as long as they are alive.

- "Stabilisation in the incidence of seizures" is primarily evidenced by clinical opinion (Appendix M), insofar as early treatment is expected to prevent any further brain damage. However, the model is not driven by seizure frequency, as seizures are not the only determinant of MoCD Type A. Developmental delay/disability, feeding difficulties and mortality are also significant manifestations of the disease. Seizure frequency does not directly influence costs or QALYs in the model, and is not explicitly modelled, although it contributes to the reduced need for nasogastric feeding (see sheet 'Healthcare Resource Use Costs' and B.3.5.3 and Section B.2.6.3).

- The "reduced need for nasogastric feeding" is presented in Section B.2.6.3 and is modelled in healthcare resource use costs only, as described above. Patients receiving fosdenopterin have a reduced need for non-oral feeding interventions, as described in the EMA Summary of Clinical Efficacy.(10) Clinical opinion sought during the clarification questions stage suggested that impaired feeding results from difficulties in oral motor skills.

- "No worsening in mobility" is also supported by clinical expert opinion (Appendix M) and is described in Section B.2.12.1. A larger proportion of treated patients were able to achieve ambulatory status without restriction, indicating improved mobility and motor capabilities.(10) The model does not explicitly capture the impact of improved mobility, as no data were available to quantify the cost or quality of life impact on patients or caregivers.

B6. Table 22 in the CS reports seven patients as having 'Present' seizure status at last assessment and a further two patients having 'Controlled' seizure status, however seizure status is not reflected explicitly in the model structure. Previous models for rare diseases that incorporate seizure frequency have included sub-models for seizure frequency, in order to capture important differences over time, across treatment arms, or a combination of

the two. Please provide an update to the cost-effectiveness model that captures this key aspect of MoCD and detail the amendment.

Although the company acknowledge the absence of seizure frequency in the model structure, it was not possible to design a model similar to other published seizure frequency-based models given the absence of data on. It was not possible to inform differential outcomes in patients with controlled vs. present seizure status, including mortality, quality of life, resource use and a transition probability between them. Furthermore, although seizure frequency is a determining characteristic of MoCD Type A, the impact of fosdenopterin is primarily on patient survival, which is fully captured using the Kaplan-Meier trial data in the model.

Efficacy and safety inputs

B7. PRIORITY. Please fix the survival modelling VBA code so that the jointly fitted generalized gamma model functions correctly, currently the treatment effect coefficient is not being incorporated as intended.

The model has been updated exclude the generalized gamma models, as recurring technical difficulties prevented the Company from accurately predicting outcomes using this model. The generalized gamma model was not considered among the best fitting distribution according to AIC/BIC scores.

Table 1: Statistical fit of parametric survival curves

Distribution	AIC	BIC
Exponential	271.1471	274.9308
Weibull	252.7185	258.394
Gompertz	252.2348	257.9103
Loglogistic	251.9912	257.6666
Lognormal	252.9157	258.5912
Gamma	254.0784	259.7539
Generalized gamma	254.31	261.8773

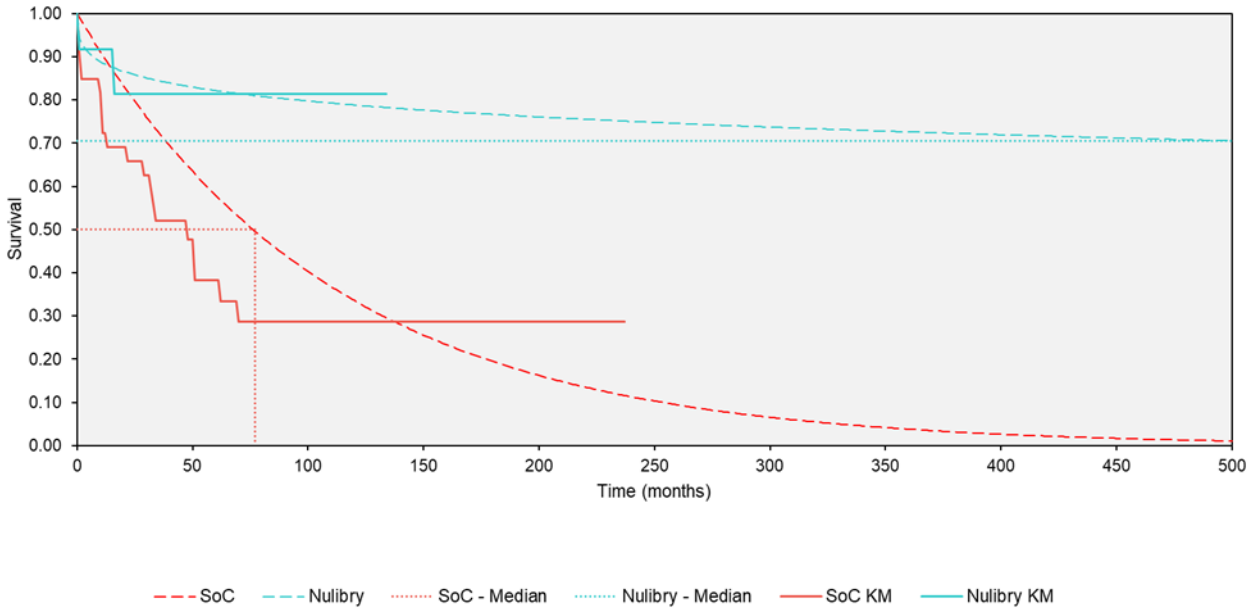
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

B8. PRIORITY. The jointly fitted survival models presented in Figure 16 of the company submission do not align with those generated by the model on the 'Settings and Results' sheet. First, the Kaplan Meier data is incomplete. Second, once the Kaplan Meier data is plotted correctly, the visual fit of the survival curves differs to what is presented in Figure 16. Please can the

company confirm which of Figure 16 or the model is correct and provide an updated version of whichever is incorrect.

As noted by the EAG, the model figure did not include the tail of the Kaplan-Meier for the SoC arm. This has been rectified in the below figure and in the model.

Figure 2: Kaplan-Meier and extrapolations for fosdenopterin vs SoC



Abbreviations: KM, Kaplan-Meier; SoC, standard of care.

B9. Please provide evidence to support the use of jointly fitted models, such as log-cumulative hazard plot and Schoenfeld plot for the proportional hazards assumption and a Q-Q plot for the constant time ratio assumption (relevant for accelerated failure time models).

In the model base-case, independently fitted parametric survival curves were used (exponential and loglogistic distributions) to inform long term survival.

As a sensitivity analysis, jointly fitted parametric survival curves were also explored. To support the use of jointly fitted survival models, we tested the proportion hazards (PH) assumption for the Cox regression model with treatment arm as a covariate. Table 2 shows the results of a hypothesis test assessing whether the beta coefficient for treatment arm differs according to time. Here, a non-significant p-value for treatment arm indicates the PH assumption is satisfied. Furthermore, the Schoenfeld residuals plot supports the PH assumption, demonstrating no deviation from a from a zero-slope (

Figure 3). A complementary log-log plot is also provided to support the PH assumption (Figure 4).

Table 2: Hypothesis test for time-varying predictors

	Chi-squared	Degrees of freedom	p-value
Treatment arm	2.12	1	0.15
Global	2.12	1	0.15

Figure 3: Schoenfeld residuals plot

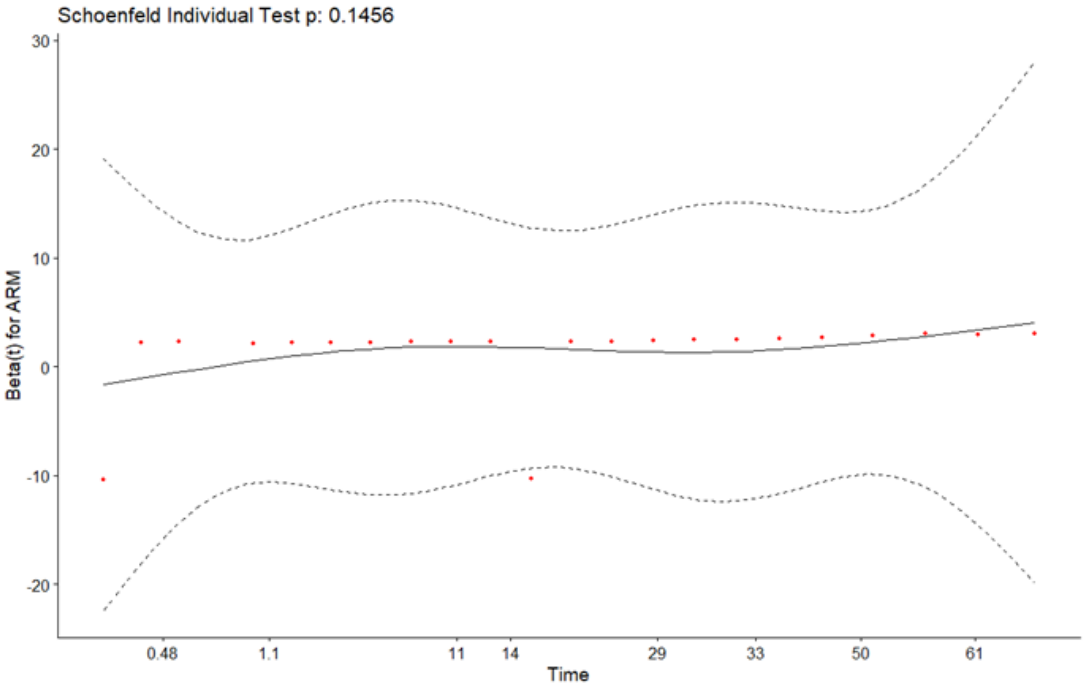
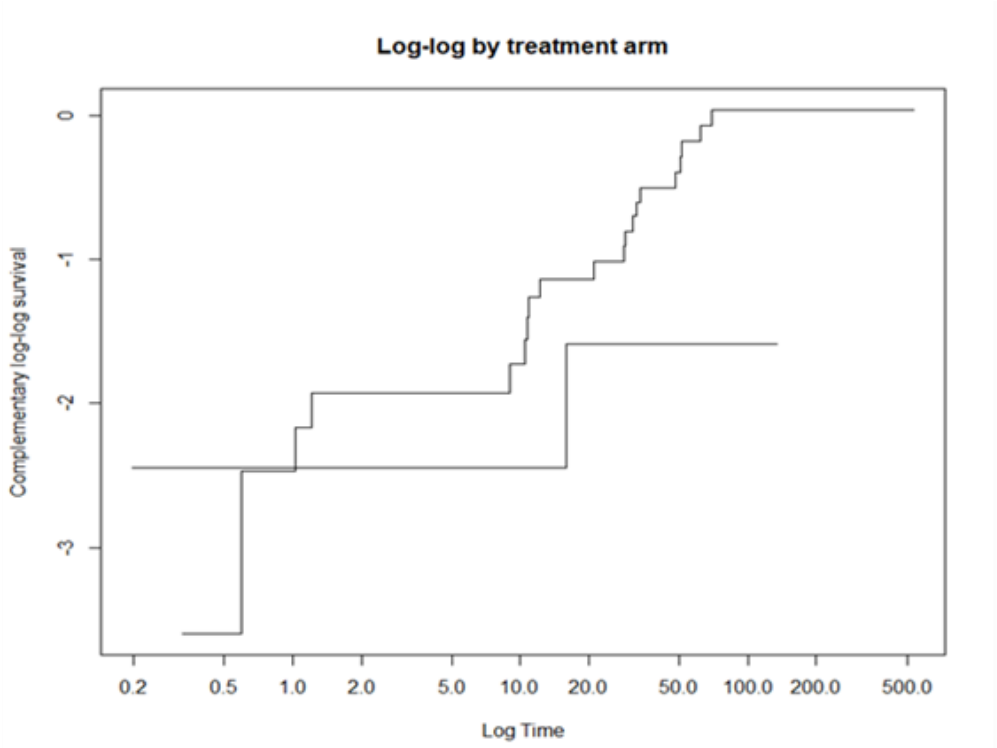


Figure 4: Log-log plot



Overall, while the diagnostic plots support the use of jointly fitted models, given the severity of the condition and reported survival of less than one year for most patients, independent models were selected to reflect published information.(7) Furthermore, as the fosdenopterin Kaplan-Meier data is shorter than the SoC data (~140 months vs ~240 months) (see Figure 2), the PH assumption is undermined by the uncertainty surrounding the tail of the Kaplan-Meier.

B10 Please can the company confirm which ONS Life Table is used to inform the model? The values included in the model do not appear to match the 2018-2020 values which are cited in the model (see cell range R3 on the 'General population data' sheet).

The Life tables have been updated to 2020-2022 UK ONS Life tables.

B11. Please can the company confirm whether the derivation of adverse event probabilities in the model are treatment *related* or treatment *emergent*?

As described in the EPAR, the single arm studies make it difficult to disentangle whether an adverse event (AE) was due to treatment with cPMP, MoCD Type A disease, its complications, or natural occurring common childhood diseases.(11) The adverse events included in the model are therefore not formally categorised as

treatment related or emergent. However, given that the most reported Treatment Emergent Adverse Events (TEAEs) in the three studies (MCD-201, 202 and 501) were in the domain of 'Infections and infestations' and in 'General disorders and administration site conditions' (mostly pyrexia and complications associated with device), it is plausible that a substantial part of the TEAEs are attributable to the complications associated with the central line used to infuse cPMP and/or to background childhood diseases. In study MCD-501, causality to treatment was only determined for serious adverse events (SAEs). In study MCD-202 there were no TEAEs assessed to be related to treatment and in study MCD-201 there were two TEAEs assessed to be related to treatment in one patient (device dislocation and catheter site inflammation).

Patient weight data

B12. Please clarify the method used to estimate [redacted] percentile weight from the NHS digital data following the period informed by WHO tables. The method used in the model appears to differ from the 10% reduction described in the CS.

As adult weight percentiles are not publicly available for England, [redacted] percentile weight was calculated using the proportional difference between [redacted] and 50th percentile weight at the last available age for children (60 months). For males, this represents a 20% decrement at [redacted] percentile vs 50th percentile, and 21% for females. A 20% decrement on the 50th percentile (median) adult weight from is then assumed from year 5 onwards to obtain the [redacted] percentile of weight in male and female adults.(12)

B13. Which source was used for patient weights following the WHO tables? The average weights for people aged 16+ seem to be from the 2019 Table 7 from the Overweight and Obesity tables (NHS digital data). Where were the

average weights for those below 16 years of age obtained from? Why were the 2021 values not used?

A correction to the model has been made following this question. As noted by the ERG, the average weights for adults 16 years onwards were taken from the NHS Overweight and Obesity tables, and those for children under the age of 60 months from the WHO. Weight for children between 4 and 16 years were updated to come from the Royal College of Paediatrics and Child Health UK-WHO growth charts 2-18 years.(13) As no tabulated data was available, the 50th percentile graphical curve was visually matched to ages 4 to 16 and applied to the model (see Table 1).

Table 1: Updated weight by age in kg

Age minimum	Age maximum	Median weight for boys	Median weight for girls
4	5	16.25 kgs	16 kgs
5	6	18.5 kgs	18.5 kgs
6	7	20.75 kgs	20.5 kgs
7	8	23 kgs	23 kgs
8	9	25.5 kgs	26 kgs
9	10	28.5 kgs	29 kgs
10	11	31.5 kgs	32 kgs
11	12	35 kgs	36 kgs
12	13	38 kgs	40 kgs
13	14	43 kgs	45 kgs
14	15	49 kgs	50 kgs
15	16	55.5 kgs	53.5 kgs

Abbreviations: kg, kilograms.

Costs

B14. In Section B.3.5.2 of the CS, the approach taken to estimate the proportion of patients receiving 'BSC' for both treatment arms is described in brief, as well as the approach taken to estimate specific use of antiseizure medication. Please can the company:

- **Clarify precisely how the estimates of [redacted]%, and [redacted]% were obtained?**
- **Clarify precisely how the weighted average of antiseizure medication use was calculated, and then combined with the aforementioned proportions to inform the model?**

The estimates for the proportion of patients on antiseizure medication was taken from the all-patient set (APS) from studies MCD-501, 201, 202 for the fosdenopterin arm and MCD-502 for the SoC arm. [redacted]

[redacted].

B15. Please can the company confirm which reported value from the Noyes *et al.,* (2013) paper was inflated to 2023 levels and used to capture palliative costs on transition to the 'dead' state? Please provide sufficient detail in this response to allow the EAG to verify the overall approach taken to obtain the final value used to inform the cost-effectiveness model.

The mean of the reported annual cost per child of £2,437 - £11,045 in Noyes et al (using 2012/13 population-based prevalence estimates) was calculated: £6,741. The Bank of England inflation calculator was used to inflate to 2021 GBP (2012 base year; £7,828).(14) This has been updated in the model to reflect the latest available year (2023) to £9,277.42.

B16. Fosdenopterin is administered as a once-daily intravenous infusion. Please can the company provide more details about how treatment is administered, including:

- **Where treatment would be administered (e.g., at home by a caregiver, or in a clinical setting)?**
- **Which costs related to treatment administration are captured within the model (including, where applicable, storage, preparation, training, and disposal costs)?**

The Summary of Product Characteristics (SmPC) for fosdenopterin specifies ‘if deemed appropriate by a healthcare professional, fosdenopterin may be administered at home by the patient’s caregiver’. Furthermore, no administration costs are applied in the model, as fosdenopterin is expected to be administered at home (injection) following the initial hospital dose. The optional cost of hospitalisation available in the model (NHS Reference Costs: Neonatal Critical Care, Neonatal Intensive Care Unit, CCU13-XA01Z) reflects all the initial acute care costs that would be incurred in the hospital setting.(15) However, as hospitalisation is expected to occur in both arms in equal frequencies, given the severity of symptoms, it is not applied in the base-case. The scenario explores the additional cost of hospitalisation in patients receiving fosdenopterin only.

B17. Cell range D38 on the 'Healthcare Resource Use Costs' sheet of the company's model includes a cost for administration hospitalisation. Please can the company explain how this cost impacts the model, including its frequency per model cycle and how this links to the frequency of treatment administration?

As described in the previous answer, the additional cost of hospitalisation applied in a scenario only reflects the initial acute care costs that would be incurred in the hospital setting (Neonatal Critical Care). This cost is not applied in the base-case.

When applied in a scenario, this cost is applied once, in the first cycle, to the proportion of patients on fosdenopterin only (see column AY in 'Outcomes Engine', from row 8 onwards – the final portion of the formula: "[…] + IF(AND(s_admincost=1, B8=1), c_admin*AD8, 0)". This cost has a small impact on results, and only impacts the ICER by +0.01% (+£96).

B18.

[redacted]

B19. Drug acquisition costs are inconsistent between the economic model and Table 41 in the company submission. The references within the economic model also suggest that the drug costs sourced from eMIT are outdated, with the costs in the model being sourced in January 2023 and eMIT last being updated in October 2023. Please provide an updated analysis including up to date drug acquisition costs.

All drug costs taken from eMIT have been updated in the economic model using the latest (October 2023) eMIT national database. Please consider the updated costs as the correct costs for the economic analysis.

B20. Healthcare resource costs are inconsistent between the economic model and Table 42 in the company submission. Many of the costs in the model have been sourced from 2020/21 NHS reference costs and the PSSRU 2021, both of which have been superseded with new versions. Please provide a revised analysis with up-to-date costs for health care resources. For costs sourced from the NHS reference costs, please include the setting that has been assumed such as outpatient, elective inpatient or non-elective inpatient. In instances where the costs are a calculated average of multiple codes, please calculate this average within the model so that the EAG can validate the calculation.

All costs have been updated to 2021/22 NHS reference costs and PSSRU 2022 and are reported in Table 3. Please consider the updated costs as the correct costs for the economic analysis.

Table 3: Updated costs

Type of cost	Unit cost	CODE
Disease management		
Nasogastric feeding (at last visit)	£61.17	N16CN
Tests		

EEG	£441.10	AA33D. Outpatient procedures, Conventional EEG, EMG or Nerve Conduction Studies, 18 years and under. Pedaitric neurology services.
Urine tests	£1.55	DAPS04. Directly Accessed Pathology Services. Clinical biochemistry.
Blood tests	£2.39	DAPS03. Directly Accessed Pathology Services. Integrated blood services
MRI	£185.81	RD01C. Diagnostic imaging. Magnetic Resonance Imaging Scan of One Area, without Contrast, 5 years and under.
CT scan	£76.41	RD20C. Diagnostic imaging. Computerised Tomography Scan of One Area, without Contrast, 5 years and under.
Ultrasound	£58.10	RD40Z. Diagnostic imaging. Ultrasound Scan with duration of less than 20 minutes, without Contrast.
Prescribing physician		
Metabolic physician	£549.62	WF01A, Outpatient consultant-led, Paediatric Inherited Metabolic Medicine Service
Specialist visits		
Nurse visit	£57.00	Section 9.2 Nurse, PSSRU 2022
Paediatrician	£228.21	WF01C, Outpatient, Paediatric consultant-led Non-Admitted Non-Face-to-Face Attendance, Follow-up
Neurologist	£231.88	WF01A, consultant-led, outpatient, Non-Admitted Face-to-Face Attendance, Follow-up.
Emergency department	£432.20	VB03Z, Emergency Care, Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment
Phone call follow-up	£135.00	Outpatient, Consultant-led, Non-Admitted Non-Face-to-Face Attendance, Follow-up
Dentist	£138.00	9.7 NHS dentist PSSRU 2022
Hospitalisation	£756.84	PR02C, Admitted patient care, Non-elective, short stay. Paediatric Epilepsy Syndrome with CC Score 0.
Institutionalisation	£1,852.00	Residential homes median cost, learning disabilities. PSSRU 2022.

Abbreviations: CC, complications and comorbidities; CT, computerised tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; NHS, National Health Service; PSSRU, personal and social services research unit.

Health-related quality of life

B21. Please can the company clarify how treatment modality impacts patient quality of life, and is there any evidence to support this? Please can the company also provide a sensitivity analysis within the model to demonstrate

how any administration-related loss of utility could influence cost-effectiveness results?

Treatment impacts quality of life by halting the progression of irreversible brain damage which leads to seizures, difficulties feeding, sitting and speaking (see Section B.1.4.5).(3, 12, 13) Unfortunately, no QoL studies were identified in the MoCD Type A SLR (Appendix H). Given the ultra-rare nature of MoCD Type A and the absence of quality of life data collected in the clinical trial programme, quality of life was approximated in the model using another condition (DS). Clinical opinion supports the assumptions applied to the model – quality of life gains in fosdenopterin recipients is dependent on when treatment is initiated, and those treated sooner tend to have better outcomes (more "normal" neurological development, ability to eat and stand and walk unaided), and thus higher QoL (see Appendix M).(16, 17)

A scenario has been added to the model to explore the additional disutility of the daily injection administration. A disutility was found for patients with bone metastases (-0.004).(18) Although these patients are not an exact match for patients with MoCD Type A, another study in patients with diabetes confirmed that the approximate disutility for injections is around -0.004 to -0.02.(19) The addition of the disutility in the fosdenopterin arm leads to a 5% increase in the ICER.

B22. Please can the company confirm the justification for the following assumptions around utility values:

- **Patients treated with fosdenopterin are assumed to have general population utility after the age of 1 (i.e., from this age, patients do not experience any loss of utility as a result of MoCD Type A), but patients still require:**
    - **One caregiver, who experiences caregiver disutility, until the patient is 5 years of age**
    - **Lifetime treatment with antiseizure medication related to the occurrence of seizures, but with no AE disutility related to seizures**

    - **Specialist visits with the frequency based on a proxy condition (Dravet syndrome [DS]), but no utility adjustments are made for seizures (despite DS being a rare, genetic epileptic encephalopathy). Additionally, the requirement for specialists visits is assumed to be the same for those on fosdenopterin and SoC, despite the difference in modelled utility**

- **Patients' carers experiencing a disutility of 0.14 due to caregiver burden and a lifetime disutility of 0.04 due to bereavement**

Quality of life in treated patients is not available from the clinical trial data or published literature. As such, the company had to assume QoL in patients treated with fosdenopterin as supported by QoL correlates using Dravet Syndrome as a proxy. These are primarily informed by clinical opinion, which suggested that quality of life is expected to near general population utilities when treated. This is supported by literature on unassisted sitting, improved mobility, and oral feeding was confirmed with a clinical expert.(17) Scenarios were included in the model to explore the impact of quality of life equivalent to 75% or 50% of general population utilities. Furthermore, data on untreated patients is so limited in the long term (given the high mortality) that it is extremely challenging to estimate QoL in later years for the SoC arm.

The model assumes that patients are treated as soon as symptoms emerge, and that the neurological damage is limited and seizures controlled with antiseizure medication. As a result, the cost of medication is incurred, but no additional QoL impact is modelled. This is also true for specialist visits, particularly the metabolic physician, who prescribes and dose-adjusts medication (as confirmed by a clinical expert, Appendix M). Other specialist visits (nurse, paediatrician, neurologist etc) were assumed to be identical in both arms as the potential differences in the frequency of consultations between arms is not documented. A conservative scenario was therefore applied. These were also validated with a clinical expert (Appendix M).

Given the need for daily injections, a caregiver disutility in fosdenopterin patients was assumed until age 5, which reflects school age in children in England. It is assumed

that following the age of 5, children who need additional care receive specialised schooling, the cost and utility of which fall outside of the scope of the economic model (i.e. societal perspective).

Given the limited data available on seizures from the clinical trials, the extent of disutility in relation to seizures (in terms of frequency, duration and severity) was too uncertain to incorporate in the model. The model is based on the assumption that immediate treatment with fosdenopterin prevents irreversible brain damage and all symptoms associated with it, such as nasogastric feeding and seizures.

Caregiver disutility (-0.14) was taken from another NICE assessment in a severe disease (multiple sclerosis) which was considered to have similar impact on caregiver QoL, in the absence of an estimate for MoCD Type A in the literature.(20) This disutility corresponds to 14.8 hours of care per day. Caring for a child with MoCD Type A is expected to have a significant toll on parents, as described by a number of commentators in the Comments on the NICE Scope (Birmingham Women's and Children's Hospital NHSFT: "the impact is a child with severe neuro-disability, requiring constant attention and high levels of caregiver input similar to nursing care", "There will be restrictions on where the family can travel to and who can look after the child.", Metabolic Support UK: "[MoCD Type A] has a negative psychosocial impact on the parent/carer, who have shared this impacts their social life, mental health and energy levels. They are often faced with little respite, relying on hospices for short term breaks and respite from care.", Willink Metabolic Unit, Manchester Centre for Genomic Medicine: "At least one full-time carer will be required 24/7.")(21)

Furthermore, the impact of child mortality is also expected to have a significant impact on parents, and a bereavement disutility of -0.04 (TA755, spinal muscular atrophy).(22) This QoL decrement has been applied from the point of mean survival in each treatment arm for the remaining time horizon, reflecting the extensive duration carers are likely to feel the loss of their child.

Sensitivity analyses

B23. Can the company please check and confirm that the PSA runs as intended and that the correct model file has been submitted, as there appears to be a copy/paste issue in the model where the values in rows 213 to 1011 contain duplicate values. Further to this, please can the company check the number of iterations required for sufficiently stable PSA results? Based on preliminary analyses performed by the EAG, the probabilistic results change markedly between runs using the default number of iterations.

- The PSA has been re-run and checked. The company recommend running the PSA in a local version to avoid these issues.

- The number of iterations has been increased to 5,000 in order to further stabilise PSA results.

B24. All the parameters varied within the PSA have an assumed standard error that is 10% of the mean value. In addition, parameters varied in the DSA appear to be assumed as either 90% or 110% of the base-case value. The EAG has identified several sources where uncertainty parameters were provided but have not been incorporated including:

- **The standard deviation of utility values provided in Lagae et al. 2018**

- **Drug acquisition costs, which are currently not captured in the PSA, sourced from eMIT**

- **Health care resource utilisation and adverse event rates derived using patient-level data and/or sourced from a clinical study report**

Please can the company review the uncertainty statistics for all model parameters subject to parameter uncertainty included in the model to ensure the sensitivity analysis results are informative? Please also sense check the distributions selected for each variable, and amend if necessary based on the updated uncertainty information.

The model has been updated with the uncertainty parameters reported in Lagae et al for utilities.(23) The uncertainty for drug acquisitions costs from eMIT have also been

captured in the model. The uncertainty for drug acquisitions costs from eMIT have also been captured in the model using +/- 10% of the mean cost. This has little influence over the ICER. Standard errors for adverse events are reported in Table 2.

We have reviewed the uncertainty statistics for all model parameters and have sense checked the distributions for each variable, including amended uncertainty information.

Table 2: Adverse event uncertainty

Event	Frequency	Standard error
General disorders and administration site condition	2.77%	4.74%
Infections and infestations	2.77%	4.74%
Gastrointestinal disorders	1.74%	3.78%
Skin and subcutaneous tissue disorders	1.74%	3.78%
Respiratory, thoracic and mediastinal disorders	1.37%	3.35%
Injury, poisoning, procedural complications	1.09%	3.00%
Product issues	0.19%	1.25%
Blood and lymphatic disorders	0.19%	1.25%
Eye disorders	0.63%	2.29%
Metabolism and nutrition disorders	0.63%	2.29%
Nervous system disorders	0.46%	1.94%
Psychiatric disorders	0.46%	1.94%
Surgical and medical procedures	0.29%	1.57%
Vascular disorders	0.29%	1.57%
Cardiac disorders	0.29%	1.57%
Ear and labyrinth disorders	0.29%	1.57%
Musculoskeletal and connective tissue disorders	0.14%	1.07%
Hepatobiliary disorders	0.14%	1.07%
Congenital, familial and genetic disorders	0.14%	1.07%
Immune system disorders	0.14%	1.07%
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.14%	1.07%

Section C: Textual clarification and additional points

C1. Please can the company share "Appendix M_CEM input validation", which is referenced in the CS but was not included within the materials?

Appendix M has been shared with the EAG for their consideration.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Metabolic Support UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Metabolic Support UK are the leading organisation for Inherited Metabolic Disorders (IMDs), supporting thousands of people worldwide through providing individual support, building communities, and continually advocating for and empowering those living with IMDs. Using qualitative and quantitative data generated via various methodologies, our small, dedicated team works to proactively identify priority needs and develop evidence-based outputs and programmes to ensure the maximum impact for individual patients, collective patient communities and the wider IMD community. Metabolic Support UK receives its funding from corporation, community fundraising and grants, trusts and giving.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the evaluation stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Metabolic Support UK received 15,700 GBP from Sciensus to contribute to Sciensus' work in understanding the MoCD type A diagnostic journey, review of their PASS study design and materials, identifying nurse-led intervention options and cross-border collaboration. This includes pass-through cost for community involvement.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information contained within this submission has been gathered through on-going discussions with families affected by MoCD type A, including through online support groups (1), resources shared by families (2-5) and a dedicated survey (6). (1) Metabolic Support UK. 2024. Molybdenum Cofactor Deficiency Support Group. Data on file. (2) BridgeBio. 2021. Elliot, living with MoCD Type A. Accessible via: https://bridgebio.com/patients-and-families/elliott/ (3) Child Neurology Foundation. 2022. MoCD Type A: A Family's Story With A Rare Genetic Disease. Accessible via: https://www.youtube.com/watch?v=Iuu5Se_jRZ8 (4) Molybdenum and more. 2021. Our Stories. Accessible via: https://molybdenumandmore.blogspot.com/ (5) Metabolic Support UK. 2023. Abdullah: Our Little Teacher. Accessible via: https://metabolicsupportuk.org/support-information/your-stories/abdullah-our-little-teacher/ (6) Metabolic Support UK. 2024. Molybdenum Cofactor Deficiency type A questionnaire. Data on file.

Living with the condition

6. What is it like to live with the condition? **What do carers experience when caring for someone with the condition?**	MoCD type A is an ultrarare, autosomal recessive inherited metabolic disorder. It is a progressive, life-limiting disease which significantly reduces life expectancy, with the majority of children born with the condition dying before they reach three years of age. Due to the condition's rareness, parents have to navigate information about what MoCD type A is, understand it and adjust their entire lives to becoming full time carers and learn how to administer different therapies throughout the day (giving medicines, managing feeding tubes, providing stimulation, stretching and massage), only to then have to start preparing for palliative and end-of-life care. MoCD type A is caused by mutations in the MOCS1 gene which interrupts the biosynthesis of molybdenum cofactor (Moco). Moco biosynthesis consists of three steps. In MoCD type A, the first step is impacted, resulting in a lack of cyclic pyranopterin monophosphate (cPMP). As a result of the lack of cPMP, insufficient Moco is produced to enable certain enzymes (sulfite oxidase, xanthine oxidase and aldehyde dehydrogenase and mitochondrial amidoxime-reducing component [mARC]) to break down toxic substances, including sulphite, S-sulfocysteine, xanthine and hypoxanthine. Sulfite is particularly toxic to the brain and high levels of this, and the other chemicals, cause the signs and symptoms of this condition. MoCD type A is generally diagnosed within the first few days or weeks of birth. Early on, newborns start showing symptoms such as excessive crying, poor feeding, excessive startle reaction and seizures (1-6): *"She showed signs of difficult feeding in the first few hours of her birth. She was taken to the NICU as doctors suspected [an] infection but later was found having non-stop seizures which lasted 4-5 mins each for 12 hours until she was prescribed sedatives." (1)* *"When he first started having seizures they looked so much like he was shivering, or trembling from crying […] When the midwife recognised he was 'jittery', as she put it, they ran all the usual blood and gas tests, had him reviewed by a doctor and sent us home. However, another sleepless night with a very distressed newborn made it clear something was definitely not right." (4)* These symptoms generally result in admittance to a hospital's neonatal or paediatric intensive care unit. Subsequently, over a period of days to weeks the baby is stabilised and diagnosed (1,6). As part of the diagnosis, families are informed that their baby has suffered severe, irreversible brain damage due to sulfite intoxication and has a limited life expectancy. Nonetheless, after several weeks, the baby will be discharged to continue to receive supportive care at home. Care at home for babies living with MoCD type A is complex and requires frequent *"unscheduled and scheduled review from A&E doctors, GPs, community doctors or specialist consultants" (4):*

	<u>Medication</u> Babies living with MoCD type A require numerous medications to improve their symptoms (1,3,4,6). Generally, babies will receive medication to control seizures, relax high muscle tone, reduce dystonia, address reflux and support bowel movements. Medication is administered, by the parent, on a regular basis, including medications which need to be administered every 6 hours, every 12 hours and every 24 hours. Especially medication that needs to be given every 6 hours has a profound impact on the lives of carers, whose sleep is interrupted. Additionally, most families have a specialised emergency seizure medication plan to enable them to control seizures at home, with the possibility of calling an ambulance if required (4,6). Other medications families have reported to require are medications to help their baby sleep, reduce the likelihood of UTIs and generally keep them comfortable (4,6). A number of families indicated that they struggle with the responsibility of frequently administering numerous medications to their child, while simultaneously recognising the need for it (4,5). Separately, families often struggled with the availability of the medications they required: *"There was always medication missing due to stock issues"* and *"We regularly had medication prescriptions cancelled without notice",* which caused additional worry and stress for families (6). <u>Feeding</u> When babies living with MoCD type A are discharged from the hospital, they are generally unable to feed (1,4,6). As a result, a nasogastric (NG) tube is fitted through which they receive their formula, which may be specialised prescribed formula to address symptoms such as constipation. Parents generally receive training from a palliative nurse on how to use the NG tube and refit it (4). Over time, a percutaneous endoscopic gastrostomy (PEG) or gastrojejunostomy (GJ) tube may be fitted to reduce symptoms such as vomiting, dehydration and constipation (1,4,6). After the age of 6 months, the baby may be introduced to a diet of blended foods, prepared by parents, in combination with milk. A number of families indicated that they have explored alternative diets, e.g. low methionine or ketogenic, to address their baby's symptoms (1,4). <u>Irritability</u> The severe brain damage experienced by babies living with MoCD type A can lead to irritability in babies living with MoCD type A (1,4). One parent shared *"The first year was definitely the hardest as he did require a lot more comforting and was often inconsolable but as time has gone on he has definitely become calmer and happier." (4).*

	<u>Seizures</u> Most babies continue to experience seizures (1,4,6). Families reported that their babies would have seizures anything from 10 to 60 times a day. One family shared *"When he is well his seizures don't generally upset him and he ends them with a smile. We didn't know that for some people seizures are actually pleasurable and it certainly appears that way quite often with him. He rarely has clustered episodes but these respond well to medication or are usually a sign he is unwell, in pain, overtired, constipated or stressed." (4)* Over time, families may experience that seizure medications no longer work or that dosages need to be changed. This is often a worrying and stressful time for families. One family shared that their baby experienced bad seizures for several days, resulting in a hospital admission and a readmission a few days later. Initially, a change in medication and morphine did not stop the seizures, but a further revision and dose increase eventually stopped the seizures. (1) <u>Oxygen therapy</u> Several families reported that over time, they noted that their baby's breathing became more laboured (1,4). Often times, this is followed by an overnight oxygen saturation study, after which oxygen may be prescribed. The prospect of oxygen therapy can be daunting for families, as it makes leaving the house even more complicated than it already is. Nonetheless, one family shared *"it has been so easy to adjust to and it is so easy to go out and about, monitor him at home and to replace oxygen cylinders by delivery. Having a SATs monitor at home to check his oxygen saturation and heart rate is also a huge help because it allows us to keep him home from hospital more and monitor any changes easily." (4)* Separately, some families have also reported their baby has had a tracheostomy to aid breathing. (1) <u>Home and life adaptations</u> Families shared that caring for a baby with MoCD type A led to numerous adaptations not otherwise required for babies (1,4,6): - To keep their baby comfortable and to be able to move around with them, as they never learn to sit up independently, families purchased a specialised car seat, bath chair, support pillow and everyday POD chair, as well as a wheelchair. - To address the additional medical needs, families bought appropriate clothing for high tone, extra warm boots and gloves for poor circulation, extra bedding and mattress protection for vomiting/tube leakages, a rucksack for medical equipment and medications, as well as gloves for medication administration.

- To allow a sense of normality and give their baby similar stimulation to other babies, families bought toys appropriate for their baby's abilities, including mobility aids for painting.

Healthcare visits

Overall, respondents to our survey indicated that the complex care needs of their baby required the involvement of many different professionals (6), including clinical nurse specialists, consultant neurologists, GPs, hospice care, metabolic consultants, ophthalmologists, palliative care, personal assistants, physiotherapists, social workers and specialist dietitians. Most of these are seen on at least a monthly basis and require families to travel to receive care; some provisions are local (e.g. GP, physio, hospice), while provisions provided by hospitals generally require longer travel (20mins - 2hours), including some provisions being spread over multiple hospitals. Visits are often planned, however, unplanned visits due to e.g. seizures are not uncommon (6).

Additionally, some families privately access additional care provisions, such as an occupational therapist, playworker, massage and aromatherapy specialist, private physiotherapist and hydrotherapist (4,6).

Fosdenopterin and MoCD type A

We are in touch with a few families (globally) who are currently receiving fosdenopterin for a child living with MoCD type A, through either a clinical trial, early/compassionate access program or previously established market access of the product. The impact of fosdenopterin on the presentation of symptoms associated with living with MoCD type A vary, which is attributable to the moment at which fosdenopterin treatment was initiated.

Families who reported that fosdenopterin was initiated before irreversible, severe brain damage was experienced by their baby, have shared that their child is doing well and that their MoCD type A does not significantly impact their life (1,2,6). They do not experience seizures, have age-appropriate mobility levels and have no pain or discomfort. They do report some issues around completing age-appropriate activities and considerations around enrolment in schools for children with additional needs. Additionally, while they do not require the same number of healthcare professionals and visits as babies who have not been treated with fosdenopterin, they do require regular visits to see their metabolic consultant, ophthalmologist and specialist dietitian, as well as additional specialties, including a speech and language therapist and visits to the developmental clinic (6). Overall, fosdenopterin has changed the lives and outcomes of these children. As one family report: *"When it's managed, which his is, they do live a normal life. And we are the product of that. And we are extremely, extremely lucky… He goes everywhere. I don't stop him from doing anything." (2)*

	Families whose baby received treatment with fosdenopterin after irreversible, severe brain damage had already been experienced, have shared that their child is doing well but that "*tak[ing] care of a child that is severely disabled"* is not easy (3). One parent shared *"when [she] was younger, she looked normal and as she got older, more medical complications occurred"*. (3) The needs of these families show similarities to those of families whose babies have not been treated with fosdenopterin: children are tube fed, require numerous medications, including for seizures, as well as continuous oxygen therapy. Numerous healthcare professionals are involved in their care and specialised equipment, such a specialised pushchairs and lifting equipment is required (1,3). Additionally, one family has reported that their child, then aged 6, required treatment for a severe scoliosis, which was crushing the child's lungs leading to repeated and continuous pneumonia. Extensive spine surgery improved the child's ability to breath and, in the parent's words, *"the absolute best decision I could have ever made for her life quality". (3)* While there are numerous similarities in terms of healthcare needs between babies living with MoCD type A who have not received fosdenopterin and those who have and continue to receive it as children; the key difference lies in exactly that, they have grown up to become children, an outcome which had not been observed in babies born with MoCD type A prior to the introduction of fosdenopterin (1,3). **Carer impact** Caring for a baby with severe brain damage has a profound impact on parents. The arrival of a new baby is supposed to be a wonderful, joyous time, during which the mother also needs to take time to recover from the birth. With MoCD type A, mother and child may be discharged from the hospital, but will soon be back in the hospital as symptoms of the condition start to present. One mother described how, two days after birth and after an *"absolute whirlwind in the hospital"* a registrar *"brought me a biscuit, having known I had just given birth and hadn't eaten all day". (4)* Similarly, families speak about parental dreams that are crushed, stipulating how they have to come to terms with their child *"never be[ing] able to walk, talk, speak or listen"*, as well as dying at a young age. (1) Parents detailed how, once their child is home after diagnosis, their day-to-day life evolves around caring for their baby, who lives with MoCD type A (6): *"During the day he required regular medications, nebuliser, suction, physio, repositioning and dystonia, seizure and vomiting management."* *"I have no social life, I haven't been out with my friends since before [he] was born. We do not trust anyone to look after [him] in the way we do."* In line with this, some parents report having had to quit their job because they *"need to care for [their child]". (6)*

	Generally, parents reported feelings of anxiety and worry, especially about the future, as well as frustration at the cards they have been dealt and the stereotype associated with babies born with complex needs: *"Often, when I tell people I have a complex needs child they immediately react as though I am facing a terrible tragedy or that my child is somehow cursed. Our reality is so far from that and I feel I can speak for myself and [him] that we don't need anyone to feel sorry for us." (4)*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Families affected by MoCD type A living in the UK reported that they were generally satisfied with the speed of diagnosis, with diagnosis happening within the first few days of life (average 3 days, range 2-4 days). Delays can occur due to the absence of specialist knowledge in e.g. district hospital, or due to births happening during bank holidays, resulting in delays in transfer to specialist hospitals or testing. While families indicated general satisfaction with speed, it is important to note that during these first few days the majority of patients did already experience irreversible brain damage. After diagnosis, the majority of people felt that there was adequate support available in case they had any questions. Nonetheless, families were disappointed to learn that treatment focussed on symptom management, with no disease-modifying treatment available. Considering care was focused on symptom management, families felt that an holistic treatment approach were missing *"I felt everything was very medication based and although medications are very useful and we are very grateful for them, they are really limited in their capacity and make our experience as parents really disempowering… There is so much we can do as parents that is hands on and not just limited to medications and symptom management." (4)* In line with this, families flagged the multitude of healthcare professionals involved in their baby's care. As stipulated previously, the complex care needs of babies living with MoCD type A require the involvement of many different professionals, including clinical nurse specialists, consultant neurologists, GPs, hospice care, metabolic consultants, ophthalmologists, palliative care, personal assistants, physiotherapists, social workers and specialist dietitians. Most of these are seen on at least a monthly basis and require families to travel to receive care; some provisions are local (e.g. GP, physio, hospice), while provisions provided by hospitals generally require longer travel (20mins - 2hours), including some provisions being spread over multiple hospitals. Additionally, families have shared that the knowledge about MoCD type A within the UK is limited. In online support groups, families refer each other to Manchester University NHS Foundation Trust as the knowledge hub on MoCD type A. Finally, it is clear that current care does not meet the needs and outcomes those affected by MoCD type A would like to see. In line with this, families expressed that improvements in care should focus on: • "More respite options, activities for the children and equipment" • "Medications to help with pain management at early stages" • "More focus on physical therapy and reducing stress for children and families"

8. Is there an unmet need for patients with this condition?	There is a significant unmet need for babies born with MoCD type A and their families. In the absence of an approved disease-modifying treatment for babies born with MoCD type A, a very limited life expectancy of less than three years will remain the standard for babies born with MoCD type A and their families. Equally, even if fosdenopterin is approved, diagnostic practices need to be improved to minimise the number of babies experiencing severe, irreversible brain damage as a result of sulfite intoxication to maximise the potential of fosdenopterin.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Fosdenopterin is the only disease-modifying treatment option for people living with MoCD type A and has the potential to make a significant impact on the lives and outcomes of people living with MoCD type A, as well as their families. Families reported that fosdenopterin has a substantial impact on the life expectancy and quality of life of their child(ren), as well as their own quality of life. Especially families who have lost a child to MoCD type A and subsequently had another child who was diagnosed with MoCD type A once fosdenopterin was available (either through a clinical trial, early/compassionate access program or previously established market access) have noted the stark differences in outcomes. Some children have now reached early teenage years and are doing well. For example, one family shared that they lost two children to MoCD type A. Because their diagnosis was known at the time their third child was born, their third child was treated with fosdenopterin from day 1 and at 12 years old is doing well, has no symptoms and attends school independently. Similarly, several other families with a child who was diagnosed within the first few days of life and subsequently initiated fosdenopterin treatment within a few hours to days after diagnosis, report similar positive outcomes. Overall, families indicated that fosdenopterin should be accessible to everyone diagnosed with MoCD type A, with early diagnosis and treatment initiation being key to obtaining maximum benefits. Other advantages of fosdenopterin shared with us by the families we support (globally) who are already receiving fosdenopterin through either a clinical trial, early/compassionate access program or previously established market access of the product, include: - Fosdenopterin is an easy medication to administer. Families either use a pump or push medication over a period of several minutes, both of which are deemed easy. - Within the UK, families reported that the delivery process of fosdenopterin is well-organised.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Disadvantages of fosdenopterin shared with us by the families we support (globally) who are already receiving fosdenopterin through either a clinical trial, early/compassionate access program or previously established market access of the product, include: - Fosdenopterin cannot reverse any brain damage suffered prior to initiation, underscoring the need to start treatment as soon as possible. - Some carers report severe vomiting as a side effect. They find the severe vomiting difficult to manage and report it involves a long process of finding the right medication that settles the stomach. - The requirement to freeze fosdenopterin at low temperatures in a medical freezer means that families are restricted in movement and cannot go on overnight breaks, holidays or travel abroad. Additionally, a family who trialled fosdenopterin opted not to continue based on the brain damage already suffered by their child, as well as the risk associated with the central line. They felt that *"the risks of a central line would not outweigh the benefits as he had already suffered extensive brain damage". (4)* Nonetheless, the majority of families whose child is receiving fosdenopterin to treat their MoCD type A reported that they felt that the benefits outweighed the risks, including in situations where the child had experienced brain damage during the first few days, weeks or months of life.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The biggest benefit is achieved when a baby is diagnosed within the first few hours to days after birth. The build up of sulfite is rapid, as is the subsequent brain damage. Brain damage is irreversible. Timely diagnosis and treatment initiation are key to achieving the maximum benefit for families affected by MoCD type A. Nonetheless, families have observed substantial benefit from fosdenopterin even when treatment was initiated several weeks or months after birth, with numerous children now living with MoCD type A beyond the age of five, where the average life expectancy used to be less than three years.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	MoCD type A is a genetic condition with a reported higher prevalence in communities where consanguineous marriage is more prevalent. Special consideration must be given to communities where consanguineous marriage is/was common.

Other issues

13. Are there any other issues that you would like the committee to consider?	Early diagnosis and initiation of fosdenopterin treatment is key to changing the outcomes of babies born with MoCD type A. Severe, irreversible brain damage often occurs within the first few days after a baby with MoCD type A is born; unless diagnostic practices are improved, babies will continue to be diagnosed after severe, irreversible brain damage has occurred.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• MoCD type A is an ultrarare, autosomal recessive, progressive, inherited metabolic disorder, which significantly reduces life expectancy, with the majority of children born with the condition dying before they reach three years of age. • No disease-modifying treatments currently exist for MoCD type A, with disease management currently evolving around supportive and palliative care. • Early diagnosis and initiation of fosdenopterin treatment is key to changing the outcomes of babies born with MoCD type A. • Fosdenopterin is the only potential disease-modifying treatment option for babies born with MoCD type A; evidence has shown significant extension of life, as well as direct impact on quality of life of people living with and those caring for someone living with MoCD type A.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Willink Unit, Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust
3. Job title or position	[redacted], [redacted] Metabolic Unit
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes
5a. Brief description of the organisation (including who funds it).	NHS Specialised Service for Paediatric Metabolic Medicine with regional remit
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to prevent or reduce brain injury with resulting disability and premature death. This is achieved by directly replacing the substrate cPMP that is required to produce molybdenum cofactor which is deficient in MoCD-type A. Fosdenopterin is a causal treatment for MoCD-A and restores the activity of molybdenum cofactor – dependent enzymes to an extent that normalises the concentration of toxic metabolites accumulating in body fluids. The treatment abolishes the disease-causing effects associated with the metabolic disorder and can effectively halt disease progression.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. Prolong life 2. Reduce the extent of brain necrosis with subsequent neurological impairment including blindness, severe spastic and dystonic tetraplegia and epilepsy. 3. Avoid lens dislocation and associated complications 4. Prevent xanthine urolithiasis
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a large unmet need because there is no other causal treatment for MoCD available

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Molybdenum cofactor deficiency type A is treated symptomatically: • anticonvulsants for epilepsy • medication to reduce spasticity and dystonia

	• tube feeding to overcome inability to swallow • oxygen supplementation or non-invasive ventilatory support to help with upper airway obstruction • Physiotherapy and care support to prevent complications emerging from immobility • Palliative care support at end of life, typically required before the age of 5 years
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no current guidelines available. The publication of an international clinical consensus guideline is anticipated in the first half of 2024 [Schwahn et al, submitted].
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is currently no defined pathway of care for patients with MoCD-A Symptomatic care is provided by multidisciplinary teams and the level of care varies depending on availability of services for complex paediatric neurodisability or palliative care. Medical care is commonly directed by paediatric metabolic specialists, paediatric neurologists or community paediatricians. Some patients are subjected to special medical diets which have limited efficacy and require nutritional monitoring. Most patients suffer from severe dystonia and cerebral palsy and require recurrent supportive acute hospital admissions to treat intercurrent respiratory illnesses, seizures or dystonic crises.
9c. What impact would the technology have on the current pathway of care?	The availability of fosdenopterin will have a large impact on current practice: - It will be imperative to provide urgent access to diagnostic tests and to the medication fosdenopterin to allow timely intervention and maximise the treatment benefit. - Once a clinical decision to start fosdenopterin treatment has been made, the biochemical response to treatment needs to be documented with repeated blood and urine tests that are only available in specialist laboratories. - Brain MR imaging is required urgently to establish the likely prognosis and to inform the discussion about the indication for long-term continuation of fosdenopterin treatment. - Once a decision has been reached to maintain the patient on long-term daily intravenous treatment with fosdenopterin, patients will require a partially implanted, surgically placed central venous line to

	administer the drug and parents/carers will have to be trained in drug administration and line care. Transition to home care may be assisted by community nursing teams. - Families of patients on long-term treatment will require ongoing assistance with transport and storage of the frozen drug and ancillaries and possibly with daily IV administration. - Patients on long-term treatment will require regular medical reviews. - Patients with a partially implanted central line will require vigilance regarding line-related infection and septicaemia. This requires visits to hospital with febrile illnesses. - Depending on the pre-existing brain injury, patients on continued treatment may still experience significant neurological disability and require multidisciplinary care support.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Current care for MoCD does not include regular IV drug administration, ongoing blood tests or frequent hospital assessments. The only comparable other (unrelated) treatment that requires long-term daily IV administration is total parenteral nutrition for persistent gut failure.
10a. How does healthcare resource use differ between the technology and current care?	See above. The use of fosdenopterin will increase healthcare resource use to enable daily IV treatment. If timely treatment can prevent severe neurodisability, the health care resources required for inpatient treatment of disability -related health problems and resources required to care for a severely disabled child in community will decrease.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Fosdenopterin can be administered in any paediatric inpatient or daycare setting, or after respective training, by home care nurses or carers at home. The treatment should be overseen by specialists in genetic metabolic disease. The decision to continue treatment long-term and the implementation and continuation of home treatment requires specialised tertiary teams with respective expertise and resources (surgical and pharmacy support).
10c. What investment is needed to introduce the technology? (For example,	Funding to expand access to rapid specialist biochemical and genetic testing. Funding for frozen storage in pharmacy and at home, for transport of the frozen product to the patient's home

for facilities, equipment, or training.)	Funding for adequate support from specialist pharmacy teams to administrate and dispense the product Funding and training for home care support will be required in some cases.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Patients will survive longer and will be able to avoid long-term ocular and renal complications. Timely treatment will reduce the burden of disability.
11a. Do you expect the technology to increase length of life more than current care?	Yes. This has been demonstrated in previous treatment trials.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. In timely treated patients, fosdenopterin prevents disability and associated morbidity and early mortality. In late-treated patients, fosdenopterin can reduce the rate of complications and distress.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Fosdenopterin will provide a biochemical normalisation in all patients affected with MoCD-A. The clinical benefit of the technology will depend on the degree of brain injury prior to initiation of treatment.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This new treatment will change the approach to affected patients completely. The current supportive and often palliative approach will shift to an urgent, highly interventional approach The diagnostic tests, skills and resources required to implement fosdenopterin treatment are available in specialist paediatric metabolic services. Access to diagnostic testing will need to be facilitated for non-specialised neonatal units to shorten the time to diagnosis. Parents/carers will require a medical grade freezer at home and respective procedures for dispensing frozen drug to the home have to be established
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Given the invasiveness and likely cost of the technology the benefit of long-term treatment needs to be weighed against the risk of daily IV drug administration, the burden of daily treatment for carers, and general resource implications of the technology. Once a biochemical response has been established, the decision to continue the treatment will largely depend on ethical and health-economic considerations, taking into account the extent of brain injury which can be assessed clinically and more accurately using brain MRI during the first few weeks of life.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-	When assessing quality of life of children with severe neurodisability it will be difficult to adequately capture the benefit of avoiding ocular or renal complications, which can create severe health problems if they occur. The incidence of acute glaucoma due to lens dislocation in MOCD-A s not known. The incidence of xanthine nephrolithiasis should be comparable or higher than in isolated Xanthinuria where it is estimated that 40% of affected individuals experience this complication during their lifetime.

adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no knows drug-related adverse effects. Complications associated with daily IV administration and use of a partially implanted central venous line are to be expected and will impact on the quality of life.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Access to and continuation of treatment were enabled within NHS institutions but there has been no support for home administration of fosdenopterin so far. Access to the clinical trials was limited to very few patients in the UK and selection of patients depended on local expertise and serendipity.

18a. If not, how could the results be extrapolated to the UK setting?	Facilitated access to fosdenopterin will increase the patient base and will likely result in more variable outcomes. The outcome of long-term treatment compared to trial data will depend on criteria of patient selection and treatment continuation.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Length of survival, incidence of ocular and renal complications, severity of motor and cognitive impairment are the main outcomes. Those were assessed in the trials, but only in a small number of patients.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Pharmacodynamic biomarkers do correlate with the incidence of ocular and renal complications. The severity of neurological sequelae will be determined by the extent of brain injury prior to starting treatment. Findings from brain imaging during the first 1-2 months after manifestation and the clinical condition at start of the treatment will largely determine whether the patient will suffer from severe neurodisability or not.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The immense benefit of treatment in some patients with early or pre-symptomatic treatment has not been adequately captured in the trial data.
20. How do data on real-world experience compare with the trial data?	The dependence of the neurological outcomes on the disease stage prior to treatment is not reflected in trial data. The incidence of renal and ocular complications has not been adequately compared to control cohorts.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Almost all known UK patients come from ethnic minority groups.
21b. Consider whether these issues are different from issues with current care and why.	There is no difference of equality issues between current treatment and treatment with fosdenopterin.

Topic-specific questions

22. Please describe how you expect treatment with fosdenopterin to be initiated. Include details of whether you expect treatment to start before or after diagnosis has been confirmed.	To be effective, treatment needs to be started as soon as there is a substantiated suspicion of a sulfite intoxication disorder (including MoCD-A, MoCD-B, MoCD-C, and isolated sulfite oxidase deficiency). Treatment can be discontinued once a diagnosis other than MoCD-A has been established or once there is no biochemical response after two weeks of fosdenopterin supplementation.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Fosdenopterin is the first causal treatment for MoCD-A • Fosdenopterin supplementation provides complete biochemical correction in MoCD-A and will prevent the occurrence of ocular and renal complications and progression of brain injury in this condition • Fosdenopterin supplementation has the potential to save a patient from severe neurodisability if given sufficiently early in the course of the disease • Effective use of fosdenopterin requires access to rapid biochemical testing and immediate access to the drug in major neonatal units. • Ethical implications of treatment continuation in patients with evidence of severe brain injury need to be carefully considered

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Fosdenopterin for Molybdenum cofactor deficiency (type a) [ID6264]

A Highly Specialised Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Author contributions

Maxwell S. Barnish	Project manager. Wrote the background and decision problem sections. Led the critique of the clinical effectiveness evidence.
Ollie Hale	Led the review of the cost effectiveness evidence. Led the EAG modelling.
Will Battershill	Contributed to the review of the cost effectiveness evidence. Contributed to the EAG modelling.
Sophie Robinson	Critiqued the company's literature searches. Managed the EAG Endnote library.
Ash Bullement	Contributed to the review of the cost effectiveness evidence. Contributed to the EAG modelling.
Jessica Owen	Contributed to the review of the cost effectiveness evidence. Contributed to the EAG modelling.
Srividya Sreekantam	Clinical expert advice to the EAG.
G.J. Melendez-Torres	Project director and guarantor.

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Abbreviations

AE	adverse event
ASM	anti-seizure medication
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CASP	Critical Appraisal Skills Programme
CDC	Centers for Disease Control and Prevention
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
cPMP	cyclic pyranopterin monophosphate
CS	company submission
CT	computerised tomography
DSA	deterministic sensitivity analysis
EQ-5D	EuroQol five dimension
EAG	External Assessment Group
EMA	European Medicines Agency
FAS	full analysis set
eMIT	electronic market information tool
GA	gestational age
GMAS	genotype-matched analysis set
GMFCS	Gross Motor Function Classification System
GMFM-88	Gross Motor Function Measure 88 Items
HRQoL	health-related quality of life
HSE	Health Survey for England
HST	highly specialised technology
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IQR	inter-quartile range
ITT	Intention-to-treat
MAA	marketing authorisation application
MoCD	Molybdenum cofactor deficiency
MRI	magnetic resonance imaging
NA	not applicable

AE	adverse event
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PEDI	Paediatric Evaluation of Disability Inventory
PenTAG	Peninsula Technology Assessment Group
PFAS	Prospective full analysis set
PSA	probabilistic sensitivity analysis
PSS	personal social services
PSSRU	Personal Social Services Research Unit
QA	quality assessment
QALY	quality adjusted life year
rcPMP	recombinant cyclic pyranopterin monophosphate
RCT	randomised controlled trial
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SLR	systematic literature review
SmPC	summary of product characteristics
SoC	standard of care
SSC	s-sulphocysteine.
TA	Technology Appraisal
UK	United Kingdom
VBA	Visual Basic for Applications
Vs	Versus
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to **Error! Reference source not found.** explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5 and **Error! Reference source not found.**.

The EAG did not consider there were any key issues related to the decision problem.

Broadly speaking the key clinical issues related to uncertainties related to i) non-randomised evidence and small sample size, ii) inconsistency of numbers included in the clinical inputs to the economic model and iii) health-related quality of life.

In terms of cost effectiveness issues, the EAG noted the key issues relate to: i) intended use in presumptive rather than solely confirmed MoCD, ii) use of fosdenopterin in the late-onset MoCD Type A population, iii) the best model to extrapolate overall survival data iv) the quality of life of patients on fosdenopterin, v) the alleviation of caregiver burden, vi) vial wastage, and vii) the ability of the cost-effectiveness model to reflect a patient's experience of MoCD Type A.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
#1	Uncertainties related to non-randomised evidence and small sample size	2.2

ID	Summary of issues	Report sections
#2	Inconsistency of numbers included in the clinical inputs to the economic model	3.2.2.6, 4.2.6
#3	Health-related quality of life	3.2.3.1
#4	Intended use in presumptive rather than solely confirmed MoCD	2.3
#5	Use of fosdenopterin in the late-onset MoCD Type A population	4.2.3
#6	The preferred model to extrapolate fosdenopterin overall survival data	4.2.6
#7	The quality of life of patients on fosdenopterin	4.2.7
#8	The alleviation of caregiver burden	4.2.7.3
#9	Vial wastage	6.2.7
#10	The ability of the cost-effectiveness model to reflect a patient's experience of MoCD Type A	4.2.2

Abbreviations: MoCD, Molybdenum cofactor deficiency.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Population	All MoCD Type A patients	Early-onset patients only	4.2.3
Outcomes on fosdenopterin	All fosdenopterin patients experience the same outcomes	Fosdenopterin patients are divided into patients that are and are not orally feeding	6.2.1
Quality of life on fosdenopterin	Patients have utility equivalent to the general population's	Orally feeding fosdenopterin patients have a utility that is halfway between SOC patient's utility and the general populations. Non-orally feeding fosdenopterin patients have the same utility as those in the SOC arm	6.2.2
Carer requirements on fosdenopterin	One carer up to the age of 5 years old, after which no support is required	Orally feeding fosdenopterin patients require the support of one carer providing 50% of full-time care up to the age of 18 years old, followed by no carer needs. Non-orally feeding patients had the same requirements as SOC patients, full time support of two carers for life	6.2.3

	Company's preferred assumption	EAG preferred assumption	Report Sections
Weight of MoCD Type A patients	Assumed to be the [redacted] percentile of weight by age	Assumed to be the 25th percentile	6.2.6
PSM to extrapolate OS for the fosdenopterin arm	Log-logistic	Exponential	4.2.6

Abbreviations: EAG, external assessment group; MoCD, molybdenum cofactor deficiency; OS, overall survival; PSM, parametric survival model; SOC, standard of care.

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology was modelled to affect QALYs by:

- Reducing the mortality rate of MoCD Type A
- Reducing the burden on care givers

Overall, the technology was modelled to affect costs by:

- Adding the acquisition cost of fosdenopterin to the treatment pathway
- Increasing survival and in turn increasing the cost of disease management over a patient's lifetime
- Reducing the prevalence of non-oral feeding

The modelling assumptions that had the greatest effect on the ICER were:

- The parametric survival model used to extrapolate overall survival data for patients on fosdenopterin
- The utility that patients experience while they are on fosdenopterin
- The long-term care giver requirements for patients receiving fosdenopterin

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify any decision problem key issues. The company decision problem was well-aligned to the NICE scope.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 1: Uncertainties related to non-randomised evidence and small sample size

Report sections	2.2
Description of issue and why the EAG has identified it as important	MoCD is a particularly rare condition. The sample sizes in the included studies are particularly small and this remains the case even in the integrated efficacy analysis pooling across studies. The individual studies are single arm or used as single arm in the pooled analysis. The overall dataset produced is akin to a non-randomised controlled trial, although not a priori designed as such. Combined with the small sample size, the non-randomised nature of the evidence increases uncertainty and opens the risk of confounding.
What alternative approach has the EAG suggested?	These issues are intrinsic to the patient population and the company's chosen positioning, so the EAG cannot resolve them.
What is the expected effect on the cost-effectiveness estimates?	There is increased uncertainty regarding clinical effectiveness inputs to the economic model, with resultant uncertainty regarding cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	These issues are mainly intrinsic to the population and decision problem. Any available additional clinical evidence, to increase the sample size, in particular randomised controlled trials, could be useful to address uncertainty about generalisability.

Abbreviations: EAG, External Assessment Group

Key Issue 2: Inconsistency of numbers included in the clinical inputs to the economic model

Report sections	3.2.2.6, 4.2.6
Description of issue and why the EAG has identified it as important	Across the clinical section, there were fluctuations in the available sample size across analyses. The EAG considered that the patient flow was not well explained and accounted for and that therefore there were uncertainties as to how the sample size for each analysis was reached. Furthermore, there were differences in the sample size used between the clinical and economic analyses. The EAG considers this to be in large part due to the use of different data cuts for the clinical and economic analyses. The survival analysis used to

Report sections	3.2.2.6, 4.2.6
	inform the economic model used the July 2019 data-cut, whereas the clinical effectiveness data used the October 2021 data-cut. The company said that the July 2019 data-cut is the latest one for which individual participant level data were available. However, the EAG could not understand this rationale, as individual participant level data would be required to present the results in the clinical effectiveness section. In the main report, the EAG provides the company's clarification on this and the EAG's comment. There was in general a lack of clarity in how the company presented information regarding sample size and data cuts used in different analyses.
What alternative approach has the EAG suggested?	The EAG reviewed the differences between the overall survival data presented in the clinical section and the data used in the economic model. The EAG concluded that there were only minor differences between the datasets and therefore it concluded that the benefit of including the data would not offset the additional uncertainty of recreating the data with only the Kaplan-Meier figure available.
What is the expected effect on the cost-effectiveness estimates?	Changes in sample size, especially when the available sample size is already small, are likely to increase uncertainty about the robustness and reliability of clinical inputs to the economic model. For example, the participants who drop out of certain analyses may have specific clinical characteristics which may explain missingness and may be related to outcomes. Similarly, the available participants for analysis at different data-cuts may differ in ways that would affect the analytical results. These sample size changes in turn increase uncertainty in the cost-effectiveness estimates presented.
What additional evidence or analyses might help to resolve this key issue?	Consistent sample size across clinical analyses and the economic modelling and/or clear justification for any sample size changes (with flow diagrams to account for all participants) would increase clarity and potentially resolve the uncertainties driving this key issue. The company could request the dataset for the October 2021 survival data from its vendor, to produce an economic model incorporating the more recent survival analysis data, as presented in the clinical effectiveness section.

Abbreviations: EAG, External Assessment Group

Key Issue 3: Evidence for health-related quality of life from clinical evidence

Report sections	3.2.3.1
Description of issue and why the EAG has identified it as important	The company did not include health-related quality of life assessment in its studies. As this is an ultra-rare condition and there have been no previous disease-modifying treatments, there are no pre-existing health-related quality of life data for MoCD (any type). Therefore, the company used health-related quality of life data from Dravet syndrome identified through a systematic review in order to generate utility values to inform the company's model. Data from a proxy condition increases uncertainty, since all conditions differ in their clinical features and resultant impact on health-related quality of life.
What alternative approach has the EAG suggested?	No utility values for MoCD are available. Therefore, the EAG was unable to use alternative sources of utility values than the company has suggested.
What is the expected effect on the cost-effectiveness estimates?	The use of utility values from a proxy condition that may not accurately match the health-related quality of life impact of MoCD Type A increases uncertainty regarding utility inputs to the model and ultimately cost-effectiveness.
What additional evidence or analyses might help to resolve this key issue?	A study focusing on health-related quality of life of treated and untreated people with MoCD would provide directly relevant evidence to address this uncertainty.

Abbreviations: EAG, External Assessment Group

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 4: Intended use in presumptive rather than solely confirmed MoCD

Report sections	2.3
Description of issue and why the EAG has identified it as important	The company states (CS Document B, Section 1.2, Table 2) that fosdenopterin is to be administered if the patient has either a confirmed genetic diagnosis or a presumptive diagnosis of MoCD Type A. The company did not model the cost of providing fosdenopterin to suspected MoCD Type A patients prior to confirmation with a genetic test. [redacted] The EAG recognises that the model is aligned with the company's expectations of clinical practice with fosdenopterin but would have liked the model to be able to explore how a change in provision may impact the cost-effectiveness of fosdenopterin.

Report sections	2.3
What alternative approach has the EAG suggested?	The EAG cannot address this within its modelling, as it is unclear precisely how many patients could potentially receive fosdenopterin with a presumptive, though later revealed to be incorrect, diagnosis of MoCD Type A.
What is the expected effect on the cost-effectiveness estimates?	[redacted]. However, the EAG understands that treatment for non-MoCD Type A patients would likely not be for a long period of time.
What additional evidence or analyses might help to resolve this key issue?	Additional information concerning the expected proportion of patients that are initiated and later revealed to be incorrectly diagnosed, as well as how long this would take to become apparent, would resolve this key issue.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MoCD, molybdenum cofactor deficiency; NHS, National Health Service

Key Issue 5: Use of fosdenopterin in the late-onset MoCD Type A population

Report sections	4.2.3
Description of issue and why the EAG has identified it as important	The final scope of this appraisal considers all MoCD Type A patients, and the company has reflected this in its base-case analysis. Following consultation with the EAG's clinical expert, the EAG understands that there are important differences in outcomes between early- and late-onset patients. Early-onset MoCD Type A is associated with greater disease severity and higher mortality. In the company's base-case analysis, all 12 patients in the fosdenopterin arm were early-onset patients, but the SOC population included a mix with 33 early-onset and four late-onset patients. A scenario exploring early-onset only patients was also included. The EAG believes that the economic evidence supporting fosdenopterin is only sufficient to make decisions related to people with early-onset MoCD Type A.
What alternative approach has the EAG suggested?	The EAG proposes comparing fosdenopterin to SOC in the early-onset population only. This means using the early-onset subgroup (N=33) of MCD-502 [1] to inform the SOC arm.
What is the expected effect on the cost-effectiveness estimates?	Cost-effectiveness estimates for fosdenopterin will improve due to the modelled outcomes of the SOC arm decreasing, reflecting early-onset MoCD Type A being more severe than late-onset.
What additional evidence or analyses might help to resolve this key issue?	A study exploring the effectiveness of fosdenopterin for the treatment of late-onset MoCD Type A would be required to supplement the data available for early-onset patients, in order

Report sections	4.2.3
	to support decision-making for the full MoCD Type A population.

Abbreviations: EAG, External Assessment Group; MoCD, molybdenum cofactor deficiency; SOC, standard of care

Key Issue 6: Extrapolation of fosdenopterin overall survival data

Report sections	4.2.6
Description of issue and why the EAG has identified it as important	The company extrapolates fosdenopterin overall survival using a log-logistic parametric survival model. This results in a low rate of mortality beyond 10 years and general-population equivalent survival from the age of 45 onwards. The EAG is concerned that this very strong assumption is driven by the tail of a KM that consists of fewer than 10 patients at two years and only four patients by 100 months (~8.3 years). The EAG believes that it is plausible for overall survival to be significantly below what the company has suggested, and true estimates could be anywhere between the company base case and parity with the SOC arm.
What alternative approach has the EAG suggested?	The company model includes an exponential model fitted to the survival data for fosdenopterin. The EAG recognises that the exponential model provides a poor fit to the observed data, but it provides insight into economic results if the survival benefit of fosdenopterin were to fall between the company base case and the survival observed in the SOC arm.
What is the expected effect on the cost-effectiveness estimates?	Overall survival is unlikely to be an important driver of cost-effectiveness estimates for fosdenopterin. Fosdenopterin is expected to be provided for life, and acquisition costs account for almost all the incremental costs of introducing the intervention into NHS practice. With long-term quality of life expected to be relatively stable, the cost-effectiveness of fosdenopterin is approximated by a ratio of drug acquisition costs to utility gained in a year versus SOC. In other words, the ratio of costs to outcomes in the long-term is approximately stable. Therefore, if fosdenopterin is considered cost-effective using one assumption for overall survival, it is likely to be cost-effective using any other assumption too. However, the assumption related to overall survival extrapolations could still affect decision making as they impact incremental QALY gains, which may in-turn influence the corresponding QALY weight for this appraisal.
What additional evidence or analyses might help to resolve this key issue?	A larger sample of fosdenopterin patients would be required to resolve this uncertainty.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; QALY, quality-adjusted life year; SOC, standard of care

Key Issue 7: Trajectory of quality of life for fosdenopterin patients

Report sections	4.2.7
Description of issue and why the EAG has identified it as important	In their base case the company assumes that a patient that is treated with fosdenopterin has general-population equivalent utility after one year of treatment. After discussions with the EAG's clinical expert the EAG recognises that there is potential for fosdenopterin patients to experience development similar to the general population's particularly if they begin treatment quickly. However, the use of anti-seizure medication and non-oral feeding in the fosdenopterin arm, along with the burden of the treatment, suggests that patients may not have the same quality of life as the population.
What alternative approach has the EAG suggested?	As mentioned in Key Issue 3, there is no health-related quality of life data for MoCD Type A patients. Given this limitation the EAG has conducted threshold analyses around the quality of life benefit of fosdenopterin.
What is the expected effect on the cost-effectiveness estimates?	The company's base-case analysis assumes that average utility for patients receiving fosdenopterin over a lifetime horizon is very close to the plausible upper bound being the age- and sex-adjusted general population, with only one year where patients are modelled to have a utility value below that of the general population. Therefore, any alternative assumption is likely to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Evidence of the quality of life of patients receiving long-term treatment with fosdenopterin could directly resolve this issue.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MoCD, molybdenum cofactor deficiency

Key Issue 8: The alleviation of caregiver burden

Report sections	4.2.7.3
Description of issue and why the EAG has identified it as important	The company assumes that MoCD Type A patients on SOC require full time care from 1.8 carers (i.e., on average, multiple carers) for the duration of their life. The company assumes that this burden is reduced to one carer when a patient receives fosdenopterin. They further assume that there are no carer requirements beyond the age of 5, when the patient enters the education system, their care becomes institutionalised and falls outside the scope of the model. At the end of

Report sections	4.2.7.3
	follow-up there were patients in the fosdenopterin arm experiencing seizure and non-orally feeding, which suggests to the EAG that these patients would still need carer support. The EAG also believes it is unlikely that a patient would be able to carry out the complex process required to self-administer fosdenopterin at the age of 5 years old. The EAG does not believe that all care requirements would become institutionalised once a patient is old enough to go to school. The EAG also believes that care provided in this setting could still be within the scope of the model given the personal and social services perspective.
What alternative approach has the EAG suggested?	The EAG prefers to assume that all patients will require some level of support until the age of 18. The EAG has also divided fosdenopterin patients into two groups of those who are and are not feeding orally. They assume that those that feed orally are in better health, require less care up to the age of 18 years old and then none beyond this. Whereas patients who feed non-orally are assumed to have the same care requirements as those in the SOC arm.
What is the expected effect on the cost-effectiveness estimates?	The company's assumptions around caregiver burden for the fosdenopterin arm are likely optimistic. Any alternative assumption (i.e., increasing the need for caregivers) is likely to worsen cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Real-world evidence of care giver burden could be used to reduce the uncertainty around this issue

Abbreviations: EAG, External Assessment Group; SOC, standard of care

Key Issue 9: Vial wastage

Report sections	6.2.7
Description of issue and why the EAG has identified it as important	Fosdenopterin is only provided in 9.5mg vials that, once opened, must be used within four hours. Given that fosdenopterin is administered daily this leads to noteworthy wastage. Using the company's base case assumptions and PAS price for fosdenopterin, the EAG estimates that there would be approximately [redacted] of discounted wastage costs over the lifetime time horizon and [redacted] in the first five years.
What alternative approach has the EAG suggested?	The EAG does not have an alternative approach to this issue, assuming that vial sizes remain as 9.5mg.
What is the expected effect on the cost-effectiveness estimates?	The wastage identified makes fosdenopterin less cost-effective than it could be if smaller and/or multiple vial sizes were available.

Report sections	6.2.7
What additional evidence or analyses might help to resolve this key issue?	Assuming no change to the vial sizes of fosdenopterin, no further evidence can resolve this issue.

Abbreviations: EAG, External Assessment Group

Key Issue 10: The ability of the cost-effectiveness model to reflect a patient's experience of MoCD Type A

Report sections	4.2.2
Description of issue and why the EAG has identified it as important	The company's model uses a simple two-state model with alive and dead health states. The outcomes of the model are therefore almost entirely dependent upon overall survival extrapolations. However, the frequency of seizures and the need for nasogastric feeding are also defining features of MoCD Type A, which are only captured in relation to simple cost outcomes.
What alternative approach has the EAG suggested?	The EAG does not believe it can formally amend the model structure to capture fosdenopterin's effect on the frequency seizures, and the impact of this on patients, with the data available. The EAG has amended the model in an attempt to capture differing rates of non-oral feeding between arms and reflect how the outcomes of patients who do and do not feed orally may differ.
What is the expected effect on the cost-effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	More granular data on the frequency of seizures in MoCD patients who are receiving SOC or fosdenopterin would be required to formally model seizure rates.

Abbreviations: EAG, External Assessment Group; MoCD, molybdenum cofactor deficiency

1.6. Summary of EAG's preferred assumptions and resulting ICER

Table 3 presents several stages in the development of the EAG base case analysis. It presents the company base case and the results of the same settings after the EAG had corrected any technical errors it identified in the company model. It then presents the results of each exploratory analyses that the EAG included in its base case. Finally, it presents the EAG preferred base case, incorporating all the corrections and scenarios simultaneously. The EAG identified a number of errors in the company submission that, once fixed, led to the ICER increasing from £[redacted]/QALY to £[redacted]/QALY. The EAG preferred base case increased the ICER further to £[redacted]/QALY.

Table 3: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost (£)	Incremental QALYs	ICER (change from company base case) (£/QALY)
Company's base case	[redacted]	18.79	[redacted]
EAG corrected company base case	[redacted]	17.51	[redacted]
Early-onset MoCD Type A population	[redacted]	19.19	[redacted]
Exponential parametric survival model for fosdenopterin OS	[redacted]	14.36	[redacted]
Fosdenopterin patients have a utility halfway between SOC patients and general population	[redacted]	14.24	[redacted]
Using the utility value for adult Dravet syndrome patients for adult MoCD Type A patients	[redacted]	18.83	[redacted]
Time to non-oral feeding to differentiate fosdenopterin patients	[redacted]	9.90	[redacted]
Patients receive more than one anti-seizure medication	[redacted]	18.79	[redacted]
SOC patients do not visit metabolic physicians	[redacted]	18.79	[redacted]
Linearly interpolate weight data for patients aged 16-25 years old	[redacted]	18.79	[redacted]
EAG's preferred base case	[redacted]	5.10	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2. BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Sentynl Therapeutics in support of fosdenopterin for treating molybdenum cofactor deficiency (type a, MoCD Type A).

2.2. Critique of company's description of underlying health problem

The company provides an account of MoCD in CS Section B.1.4. The EAG considered this description to be accurate.

MoCD is a rare genetic inborn error of metabolism. This affects the synthesis of molybdenum cofactor, which is crucial for preventing toxic build-up of sulphite in the brain.[2] MoCD has three types – A, B and C. While each is related to a different genetic mutation in the molybdenum cofactor synthesis pathway, they are clinically indistinguishable and all involve the accumulation of toxic metabolites, including sulphite.[3,4] MoCD Type A is the most common type[3] and arises specifically from pathogenic variants of the *MOCS1* gene, which is responsible for the conversion of guanosine triphosphate (GTP) to cPMP.[5] The lack of active sulphite oxidase causes an increase in central nervous system (CNS) sulphites, SSC in particular that leads to irreversible neuron degeneration and CNS damage and, in most cases, early death. [3,6-8]

Limited epidemiological information is available on MoCD. According to the company, only about 100 cases of this condition (all types) have been described in the literature. Even taking into account potential under-diagnosis due to low familiarity with the condition, MoCD is an ultra-rare condition. The incidence of MoCD[9] has been estimated as between one in 341,690 and one in 411,187. Cases described in the literature are found in a variety of ethnic groups with higher incidence in areas of high consanguinity. [10-13] Clinical advice to the EAG was that consanguinity was a key risk factor for MoCD and is present in the majority of cases. While ethnicity itself does not genetically predict MoCD risk, clinical advice to the EAG was that in a UK context, MoCD is most common in Asian communities within areas such as the West Midlands and Greater Manchester, due to high levels of consanguinity in the population. It was advised that international evidence is likely to generalise well to a UK setting as the key risk factors, such as consanguinity, were seen as applying consistently across countries.

No UK epidemiological profile for MoCD is available. The CS states that to the company's knowledge there is one living person with MoCD in England. Clinical advice to the EAG was that this is correct, although there have been previous patients who have died due to the short life expectancy of MoCD. The EAG noted that this may not provide a stable and suitable patient base for NICE guidance. Clinical advice to the EAG was that further patients may be identified over the coming years through the introduction of whole genome sequencing through public health and NHS England, which may address some of the uncertainty about a suitable patient population.

A systematic review[7] showed that 73% of people with MoCD presented symptoms within 28 days of birth and 46% on the first day of life. It also showed that symptom presentation can be variable with the most common initial symptoms being intractable seizures (72%), feeding difficulties (26%) and truncal hypotonia (11%). A natural history study specifically of MoCD Type A found median age of symptom onset to be two days (range one to 927[3]) with the most common presenting symptoms being seizures (93%) and feeding difficulties (85%). Intracranial haemorrhage was a presenting symptom for 7% of patients. Progressive brain damage associated with MoCD results in severe clinical burden. The vast majority (92%) of participants in an international retrospective cohort study[3] developed at least one disease sequela during follow-up, the most common being limb hypertonicity (88%), developmental delay (85%) and truncal hypotonia (71%). International mortality data[3] for MoCD Type A show median survival of 4.23 years. This study also shows that among people with neonatal onset MoCD Type A, 72% survive to one year of age with a median age at death of 2.4 years. Clinical advice to the EAG was that survival for early onset MoCD Type A in the UK (where no disease modifying treatment is currently available) is typically only about two years from birth.

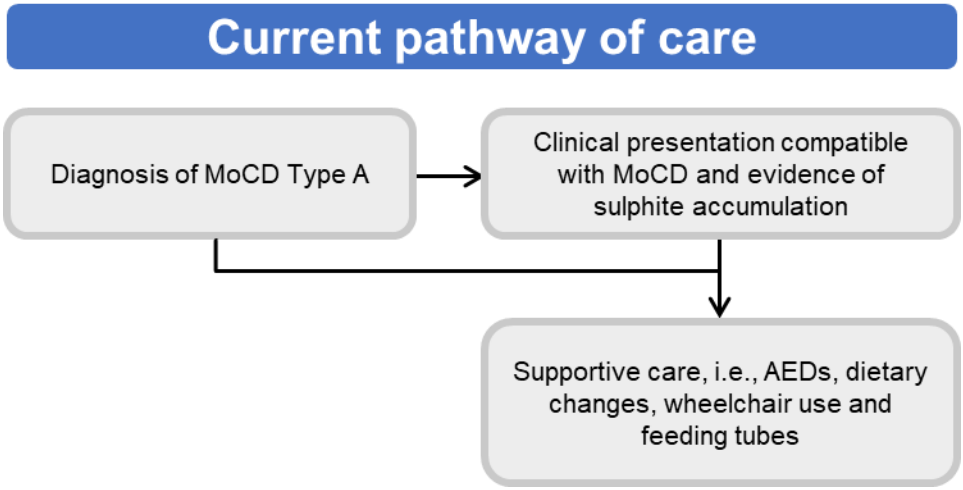
2.3. Critique of company's overview of current service provision

There are currently no clinical guidelines on MoCD Type A in England or internationally. Current practice is uncertain and is likely to be tailored to the individual patient rather than a standard of care. The lack of licenced disease-modifying treatments necessitates a focus on best supportive care, including symptom relief and support for the patient. Best supportive care does not address the underlying mechanisms of disease and does not improve survival prospects. The current pathway of care is summarised in Figure 1.

Clinical advice to the EAG was that there are no disease-modifying treatments available for MoCD Type A in the UK. Any available treatments are purely focused on symptom relief. These

treatments may include feeding tubes, wheelchairs and dietary changes – although clinical advice to the EAG was that dietary changes, such as restricting sulphur-containing amino acids, have not been particularly successful. Clinical advice to the EAG was that almost all early-onset MoCD patients would receive anti-epileptic medication, typically a combination of many anti-epileptic medications in an attempt to gain seizure control. Treatment would typically invoice a multi-disciplinary team, including a neurologist, paediatrician and allied health professionals, and be highly resource-intensive, despite limited treatment efficacy.

Figure 1. Current pathway of care



Source: CS Document B Section 1.5, Figure 6. AED, anti-epileptic drug(s).

Fosdenopterin is a substrate replacement therapy intended to address the underlying cause of MoCD Type A. Fosdenopterin was given orphan designation by the European Medicines Agency (EMA) on 20th September 2010 (EU/3/10/777) and was approved by the EMA in September 2022.[14] [redacted]. The EMA recommendation for fosdenopterin was for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A. [redacted]The intended mechanism of administration for fosdenopterin is intravenous. Fosdenopterin is intended for administration at an infusion rate of 1.5 mL/min after reconstitution with 5 mL of sterile water for injection. If deemed appropriate by a healthcare professional, fosdenopterin may be administered at home by the patient's caregiver. The healthcare professional should calculate and provide the volume of fosdenopterin in millilitres (mL) and the number of vials needed for each dose to the caregiver/patient.

In patients less than 1 year of age, the recommended dose of fosdenopterin is titrated based on gestational age. For patients less than 1 year of age who are preterm neonates (gestational age <37 weeks), the recommended starting dose of fosdenopterin is 0.40 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months. For patients less than 1 year of age who are term neonates (gestational age ≥37 weeks), the recommended starting dose of fosdenopterin is 0.55 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months. For the paediatric population from 1 year to less than 18 years of age and adults, the recommended dose is 0.90 mg/kg administered intravenously once daily.

The company states (CS Document B, Section 1.2, Table 2) that fosdenopterin is to be administered if the patient has either a confirmed genetic diagnosis or a presumptive diagnosis of MoCD Type A. The four key studies that form the integrated efficacy analysis differ in their diagnostic inclusion criteria. MCD-201 required a confirmed genetic diagnosis, whereas the other studies accepted clinical and/or biochemical symptoms as an alternative diagnostic. The EMA indication,[14] [redacted] states that 'Fosdenopterin is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.' The SmPC says that any patients with a presumptive diagnosis have to have a genetic test to confirm the diagnosis. While this information was not in the CS, the company has clarified that all participants within the integrated efficacy analysis had positive genetic tests for the target condition, although this may be after the initiation of fosdenopterin therapy. .

2.4. Critique of company's definition of the decision problem

The company's statement of the decision problem is provided in Table 4. The EAG considered that the company's decision problem was well-aligned with the NICE final scope[15] for this appraisal and had no concerns related to the decision problem.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with MoCD Type A	People with MoCD Type A	NA	NA
Intervention	Fosdenopterin	Fosdenopterin	NA	NA
Comparator(s)	Established clinical management without fosdenopterin	Established clinical management without fosdenopterin	NA	NA
Outcomes	The outcome measures to be considered include: • Overall survival • Cognitive function • Gross motor function • Adverse effects of treatment • Body weight and nutritional parameters (including growth and development) • Neurological development parameters • Frequency of seizures • Mortality • Severity of disease	The outcome measures to be considered include: • Overall survival • Cognitive function • Gross motor function • Adverse effects of treatment • Body weight and nutritional parameters (including growth and development) • Neurological development parameters • Frequency of seizures • Mortality • Severity of disease	NA	Health-related quality of life was included in the company decision problem. However, the company did not have any available data on this outcome in MoCD.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Health-related quality of life (for patients and carers)	• Health-related quality of life (for patients and carers)		
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.	A cost-utility analysis will be presented, as per the reference case. The cost-effectiveness of fosdenopterin compared with standard of care will be expressed in terms of incremental cost per quality-adjusted life year. The time horizon will cover the entire lifetime horizon, as fosdenopterin is a life-extending therapy. Costs will be considered from an NHS and Personal Social Services perspective. Any commercial arrangements will be included in the analysis.	NA	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Subgroups	No subgroups were listed on the NICE scope.	No subgroups were listed on the company decision problem.	NA	NA
Special considerations including issues related to equity or equality	No specific concerns related to equity or equality were listed on the NICE scope.	No specific concerns related to equity or equality were listed on the company decision problem.	NA	NA

Abbreviations EAG, External Assessment Group; NA, not applicable; NICE, National Institute for Health and Care Excellence

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) in March 2023 (updated in November 2023) to study the treatment landscape regarding clinical efficacy and safety of treatments for MoCD Type A. As profiled in Table 5, the EAG was generally satisfied with the quality and reporting of the company's SLR.

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D, Section 3.2	The searches were carried out in a good variety of sources. No subject headings were used for most of the search terms (Table 11, lines 1, 2 & 4) which is not best practice. Truncation and adjacency operators were not used, which would have expanded the search. The main search was combined with a varied collection of terms, the purpose of which is not clear (Table 11, lines 4 & 5). The company did not provide a narrative description of the search structure and terms used, so it is not possible to identify the thinking behind the different sections of the search. Line 4 appears to be a loose collection of different study types, but these have not been searched systematically and no tested search filter (e.g. the RCT filter in the Cochrane Handbook[16]) has been used to identify particular study types. It is likely that some relevant records may have been missed.
Inclusion criteria	Appendix D, Section 3.1	The EAG considered the inclusion criteria to appropriately encompass the decision problem.
Screening	Appendix D, Section 3.3	Two reviewers assessed all citations. Any disagreements were resolved through discussion with a third reviewer. The EAG considered this to be good process to minimise selection bias.
Data extraction	Appendix D, Section 3.3	Data extraction was conducted by a single reviewer. Validation was performed by a second senior reviewer. It was not stated if this was independent review, or whether the second reviewer had sight of the initial reviewer's scores. The EAG considered this might lead to risk of bias. Any disagreements were referred to the project manager and resolved through discussion.
Tool for quality assessment of included study or studies	Appendix D, Section 4.3	Quality assessment was conducted using the JBI Critical Appraisal Checklists for Cohort Studies, Textual Evidence Narrative (for reviews) and Case Series, as appropriate to the study design of included studies. The EAG considered this appropriate. The company noted

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		that as many available studies were conference abstracts, reporting was limited. However, it was not stated whether a second reviewer undertook quality assessment and if this was conducted independently. The EAG considered this might lead to risk of bias.
Evidence synthesis	CS Document B.2.8 and B.2.9	No meta-analysis or indirect treatment comparisons were included in the company submission. The company presented integrated clinical results pooled from three studies on fosdenopterin or rCMP and one natural history study in MoCD Type A. The EAG broadly considered this appropriate.

Abbreviations: EAG, External Assessment Group; MoCD, molybdenum cofactor deficiency; rCMP, recombinant cyclic pyranopterin monophosphate.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

A total of 18 studies met the inclusion criteria for the company's SLR, as profiled in Table 4 in the CS Document B Section B.2.1. Of these 18 studies, 11 were case reports, four were case series, one was a prospective cohort study, one was a comprehensive review, and one was a retrospective natural history study.

The company identified four key studies to pool in its integrated efficacy analysis. As it was considered unethical to conduct a placebo-controlled trial in this population considering the rarity of disease and lack of treatment options, the company created a control cohort in MCD-502, a retrospective and prospective natural history study. In describing the trials, the company refers to fosdenopterin as cPMP (cyclic pyranopterin monophosphate), to reflect that cPMP and recombinant pyranopterin monophosphate (rcPMP) have the same active moieties. The company considered rcPMP data to be directly relevant to the decision problem though rcPMP is not fosdenopterin per se. Due to equivalence, the EAG did not consider this a key issue.

Table 6 provides an overview of the four key studies included in the company's integrated efficacy analysis. The company creates a non-randomised comparative study in the integrated efficacy analysis with MCD-502 as the control arm (natural history) and the intervention arm comprising pooled data from MCD-501, MCD-201 and MCD-202. While the EAG refer to this as the fosdenopterin arm, it should be noted that study MCD-501 uses rcPMP as the intervention rather than cPMP.

Table 6: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Reported outcomes related to decision problem
MCD-501[17]	A retrospective, observational, noninterventional data collection study	Paediatric patients with MoCD Type A, N=4	rcPMP	NA	• Survival • Growth parameters • Disease characteristics and progression • Feeding patterns • Neurologic examination • Developmental assessments • Safety • Biomarkers • Neurophysical development • Ophthalmologic and hearing assessments • Neuroimaging for anatomical development
MCD-201[18]	A Phase 2, multicentre, multinational, open-label, dose escalation study	Paediatric patients with MoCD Type A, previously treated with rcPMP, N=8	cPMP	NA	• Change from baseline in urine and blood SSC levels • Change from baseline in clinical findings from neurological examination • Change from baseline in age-appropriate motor and cognitive assessments • Change from baseline in seizure frequency • Changes in growth parameters

Study name and acronym	Study design	Population	Intervention	Comparator	Reported outcomes related to decision problem
					• Change from baseline in feeding patterns • Change from baseline in neuroimaging • Change from baseline in MoCD-associated urine and blood biomarker levels including, but not limited to, uric acid and xanthine
MCD-202[19]	A Phase 2/3, multicentre, multinational, open-label study	Paediatric patients up to 5 years of age with confirmed or suspected MoCD Type A, N=3	cPMP	NA	• Overall survival • Changes from baseline in MoCD Type A-related biomarkers • Changes from baseline in growth parameters • Change from baseline in feeding patterns • Change from baseline in age-appropriate motor and cognitive assessments • Neurologic examination • Time course of clinical evidence of seizure activity • Change from baseline in brain ultrasound imaging (neonates only) • Change in brain MRI findings • Ophthalmologic examination
MCD-502[1]	Natural history study, retrospective and prospective,	Paediatric patients with	Natural history	NA	• Survival at 1 year of age for patients with MoCD Type A • Growth parameters

Study name and acronym	Study design	Population	Intervention	Comparator	Reported outcomes related to decision problem
	multinational, multicentre	MoCD Type A, N=37			• Weight • Height • Seizure activity • Neurologic assessments • Neurocognitive and development assessments • Feeding patterns • Clinically significant medical events • Biochemical markers • Head circumference • Neuroimaging findings • Physical examination • Vision and hearing assessments

Abbreviations: cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; MRI, magnetic resonance imaging; NA, not applicable; rCPMP, recombinant cyclic pyranopterin monophosphate; SSC, s-sulphocysteine.

Source: Adapted from CS Document B Section 2.2, Table 5.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design and conduct of the studies

The four key studies[1,17-19] included in the company's integrated efficacy analysis were all small (sample size ranging from three to 37, the largest being for the natural history study of non-treated patients) non-randomised observational studies. Given the rare nature of MoCD Type A, the EAG did not consider this surprising. The largest study in the 'fosdenopterin arm' of the pooled study for the integrated efficacy analysis contributed eight patients to the pooled analysis, with a total of fifteen unique participants in the fosdenopterin arm of the pooled efficacy analysis. All four studies included UK recruitment, although – potentially due to low participant numbers and risk of identification – it was not stated how many participants from the UK were included.

3.2.2.2. Population

Trial eligibility criteria

Table 7. Key inclusion criteria for the pivotal studies

Study number	Main inclusion criteria
MCD-501[17]	Included male and female patients of any age with MoCD Type A, suspected Type A, or Type B who previously received rcPMP only by IV route of administration and for whom parents or legal guardians voluntarily provided written informed consent
MCD-201[18]	Male or female patients with a genetically confirmed diagnosis of MoCD Type A (MOCS1 mutations) Currently treated with rcPMP infusions through named-patient use with rcPMP
MCD-202[19]	Male or female neonatal (1 to 28 days of age, inclusive, at the time of fosdenopterin administration, with Day 1 of age corresponding to the Day of birth), infant (29 days to < 2 years of age) or child patients (2 to 5 years of age [inclusive]) with MoCD Type A, previously untreated with fosdenopterin or treated with fosdenopterin through the compassionate use In neonates, diagnosis of MoCD Type A, based on: Prenatal genetic diagnosis, or Onset of clinical and/or laboratory signs and symptoms consistent with MoCD Type A (e.g., seizures, exaggerated startle response, high-pitched crying, truncal hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulphite and/or SSC, elevated xanthine in urine or blood, or low or absent uric acid in the urine or blood) within the first 28 days after birth In infants or children, diagnosis of MoCD Type A, based on: Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may have been obtained after initiation of fosdenopterin therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A
Study MCD-502[1]	Both living and deceased patients of any age were considered for study inclusion. Main inclusion criteria: Documented clinical and biochemical diagnosis or genetic diagnosis of MoCD or isolated SOX deficiency. Biochemical criteria were either 1) high urine, serum, or plasma levels of SSC or 2) a positive urine sulphite dipstick in at least two samples

Key eligibility criteria for the pivotal studies are shown in Table 7. The EAG considered the inclusion criteria to be well-aligned to the decision problem.

Baseline characteristics

Baseline characteristics for the integrated efficacy analysis are presented below in Table 8.

Table 8. Baseline characteristics for the integrated efficacy analysis

	cPMP-treated patients (n=15)	Untreated controls (full analysis set, n=37)	Untreated controls (genotype-matched analysis set, n=19)
Gender, male, n (%)	7 (50.0%)	28 (75.7%)	13 (68.4%)
Race, white, n (%)	11 (73.3%)	21 (56.8%)	12 (63.2%)
Gestational age, mean (SD)	38.3 (1.65)	39.0 (1.19)	39.0 (0.90)
Age at onset of MoCD symptoms, days, mean (SD)	1.5 (1.16)	55.1 (192.70)	16.6 (50.83)
Presence of seizures, n (%)	10 (71.4%)	34 (91.9%)	18 (94.7%)
Presence of feeding difficulties, n (%)	9 (64.3%)	31 (83.8%)	17 (89.5%)

Source: adapted from CS Document B Section B.2.3.7, Tables 11 to 13.

The EAG considered that the baseline characteristics were generally well-balanced between groups, although noted that age at symptom onset was much greater in the historical control group than in cPMP-treated patients. Parental consanguinity was reported in 50% of treated patients and 67.6% of untreated controls. Clinical advice to the EAG was that this is likely to generalise to a UK context, especially in localities with a high density of people of Asian cultural origin, such as Greater Manchester and the West Midlands. The advice was that MoCD is not specifically genetically associated with being Asian, however since consanguinity is much more common among culturally Asian communities, this leads to the risk of having MoCD being positively associated with Asian ethnicity.

3.2.2.3. Intervention

In studies MCD-201[18] and MCD-202,[19] the intervention was cPMP, which is fosdenopterin. In study MCD-501,[17] the intervention instead was rcPMP. This is not fosdenopterin per se but is considered to have identical active moieties to fosdenopterin. Clinical advice to the EAG was that this was not a concern because the mechanism of action of cPMP and rcPMP is the same.

With regard to fosdenopterin dosing, in MCD-201,[18] daily IV fosdenopterin infusions began on day one, dose-matched to the participant's current rcPMP dose. In MCD-202,[19] dosing began as soon as possible after birth for neonatal participants and was based on a patient's gestational age. Day one dosing for term (≥37 weeks GA) and preterm (<37 weeks GA) neonates began with fosdenopterin IV infusions of 700 and 525 µg/kg/day, respectively. For all patients, the first

dose adjustment was scheduled to take place at day 28 with incremental increases up to 1300 µg/kg/day by month 9.

3.2.2.4. Comparator

None of the key included studies was comparative. Natural history study MCD-502[1] formed the 'control arm' of the pooled study for the integrated efficacy analysis.

3.2.2.5. Outcomes

An overview of outcomes available within the key evidence landscape is summarised in Table 9. The company describes it in CS Table 9 as the evidence base for fosdenopterin, although it should be noted that in MCD-501,[17] the intervention was rcPMP, while MCD-502[1] was an untreated natural history study. The EAG could not identify any minimally clinically important differences (MCIDs) for scoped outcomes in a MoCD population. The EAG did not consider that using MCIDs from proxy conditions would be useful in this context.

The EAG considered the measures used to assess outcomes to be relevant and appropriate to the population and condition being studied. The outcomes broadly cover the breadth of the NICE scope[15] for this appraisal, with the exception of health-related quality of life, which was not assessed by any studies. There was no specific cognitive assessment, although global development scales were used and neuroimaging data provide insight into brain function.

3.2.2.6. Statistical analysis

There were three analysis populations defined for the integrated efficacy analysis:

- Full analysis set (FAS) – all participants with MoCD Type A, treated and untreated
- Prospective full analysis set (PFAS) – all participants with MoCD Type A, treated and untreated, within studies MCD-201,[18] MCD-202, and MCD-502,[1] who were followed prospectively
- Genotype-matched analysis set (GMAS) – all participants with MoCD Type A who were included in genotype matching between treated patients and untreated natural history controls

Genotype matching for the GMAS was conducted using a matching algorithm. Treated patients are matched with patients in the natural history study who have the same homozygous

mutation. If a treated patient had more than one control in the natural history study with the same homozygous mutation, the treated patient was matched to each in a one-to-many fashion. Treated patients who did not have an exact natural history homozygous match were matched upon mutations with a similar anticipated impact on protein function. If a treated patient did not have an exact natural history homozygous match but did have more than one match with a mutation with a similar anticipated impact on protein function, the treated patient was matched to each in a one-to-many fashion.

The EAG noted that matching was conducted in a deterministic (i.e. 'manually') rather than probabilistic manner (e.g. via propensity scores). Matching would typically be probabilistic unless it was simply, for example, based on age and sex. The matching methods used by the company are generally straightforward, although they do use a series of sequential steps, which the EAG considered would not be typical of deterministic matching. Clinical advice to the EAG supported the appropriateness of the matching approach, based on the ultra-rare status of MoCD, the consequent impossibility of finding an exact mutation match for all patients, and the fact that mutations impacting on protein function are pathogenic and it is very relevant to consider these in the analysis.

The EAG considered FAS to be the most appropriate analysis set to make best use of the available data and maximise sample size within the context of an ultra-rare condition.

The company presented integrated clinical results pooled from three studies on fosdenopterin or rCMP and one natural history study in MoCD Type A. The pooled analysis was used to present clinical effectiveness findings in the CS rather than presenting the results of individual studies.

The EAG considered pooling results from separately designed studies is subject to many limitations. However, there were just as many issues, if not more, with meta-analysing a series of small studies. Pooling facilitated a larger sample size for integrated efficacy analyses. In response to clarification question A1, the company explained that integrating the analysis across three cPMP studies and one natural history study was conducted in order to provide a robust analysis to interpret the effect of cPMP in the target population and compare outcomes with untreated controls, overcoming small sample sizes issues associated with an ultra-rare condition, heterogeneity of disease presentation and the mix of prospective and retrospective data collection. The EAG generally agreed with this rationale, although did not agree that pooling prospective and retrospective data would overcome the challenges posed by this methodological difference. On balance, the EAG did not consider this to be a key issue.

Table 9 provides an overview of outcomes available within the evidence base and how they are analysed. The EAG noted minor inconsistencies between the methods and results sections of the CS; in particular not all analyses presented in the results were clearly specified in the methods. The EAG was satisfied that outcome presentation was generally well aligned to the decision problem. Within each outcome domain, for example MoCD-associated biomarkers, all measures were presented for the same combination of analysis sets.

Table 9. Overview of outcomes available within the evidence base

Outcome	Description	Analysis sets and effect measures
Survival status	Survival status was determined in all four key studies (MCD-201,[18] MCD-202,[19] MCD-501,[17] MCD-502[1]). Overall survival was defined as the interval in months from date of birth to the date of death or date last known alive.	FAS. GMAS using: i) unadjusted methods, ii) adjusted analysis by matched ID, iii) inversely weighted analysis. Median OS estimated for untreated patient group (not estimable for treated group due to low number of deaths). Survival probabilities (%) at one, two and three years of age. KM curves. Cox proportional hazards models with hazard ratio.
MoCD-associated biomarkers	MCD-201,[18] MCD-202[19] and MCD-502[1] assessed SSC, uric acid and xanthine in urine and plasma. MCD-501[17] assessed SSC, uric acid and xanthine in urine only.	FAS and GMAS. Mean biomarker levels. Box plots.
Growth	MCD-201,[18] MCD-202,[19] MCD-501[17] and MCD-502[1] all assessed weight, length/height and head circumference.	FAS. Individual and aggregate patient plots presented for percentiles and z-scores, based on WHO curves for children up to 5 years and CDC curves for children above 5 years. Mean and median z-scores.

Outcome	Description	Analysis sets and effect measures
Feeding patterns	MCD-201[18] and MCD-202[19] assessed current feeding patterns. MCD-501[17] and MCD-502[1] assessed predominant and all feeding patterns. All studies assessed oral and nasogastric feeding types and had an 'other' category. MCD-501[17] subdivided further into oral feeding and oral suck. MCD-201,[18] MCD-202[19] and MCD-502[1] assessed gastronomy tube as a feeding type, while MCD-501[17] assessed percutaneous endoscopic feeding.	FAS and GMAS. Frequency and percentages of each feeding method at the last visit where feeding pattern was recorded. Oral vs non-oral analysed using logistic regression with odds ratio as the outcome. Median time to sustained non-oral feeding. How many times more likely treated patients were than untreated patients to be feeding orally at the last assessment (with hazard ratio).
Developmental and functional assessments	MCD-201,[18] MCD-202,[19] MCD-501[17] and MCD-502[1] all assessed GMFCS-ER, Bayley-III, WPPSI and ability to sit unassisted. MCD-501[17] and MCD-502[1] also assessed Denver. MCD-202[19] also assessed GMFM-88 and PEDI.	PFAS (referred to as Partial FAS not Prospective FAS in this part of the CS – the company has confirmed this should have been Prospective FAS) and FAS. Gross motor function GMFCS-ER Levels (ordinal). Percentage at Level 5 (non-ambulatory). Bayley and WPPSI age-equivalent scores. Percentage unassisted sitting.
Neuroimaging	MCD-202,[19] MCD-501[17] and MCD-502[1] assessed MRI, CT scan and ultrasound data. MCD-201[18] assessed MRI and CT scan data.	FAS, PFAS and GMAS. Normal vs abnormal imaging results – shown by percentage.

Outcome	Description	Analysis sets and effect measures
Seizure activity	MCD-501[17] and MCD-502[1] assessed seizure counts. MCD-201,[18] MCD-202,[19] MCD-501[17] and MCD-502[1] (only for prospective data collection) assessed seizure type.	FAS and PFAS. Percentage ongoing seizures. Percentage seizures controlled on anti-epileptic drugs. Difference in likelihood of treated and untreated patients having seizures not present or resolved versus having seizures controlled or continuing, with odds ratio. Percentage, number and type of concomitant anti-epileptic drugs.
Neurological examination	MCD-201,[18] MCD-202,[19] MCD-501[17] and MCD-502[1] assessed spontaneous movement, truncal tone, appendicular tone, deep tendon reflexes and primitive reflexes. MCD-201,[18] MCD-202[19] and MCD-501[17] additionally assessed dystonic, opisthotonic and clonus parameters. MCD-201[18] and MCD-502[1] additionally assessed ambulation and communication parameters.	FAS, PFAS and GMAS. Normal vs abnormal neurological results – shown by percentage.

Abbreviations: CT, computerised tomography; Denver, Denver Developmental Screening Test; GMFCS-ER, Gross Motor Function Classification System, Expanded and Revised; GMFM-88, Gross Motor Function Measure 88 Items; MRI, magnetic resonance imaging; PEDI, Paediatric Evaluation of Disability Inventory; SSC, s-sulphocysteine; WPPSI, Wechsler Preschool and Primary Scale of Intelligence. Subgroups are not included in this table, as sub-group analysis is handled at the end of Section 3.2.3.1.

Source: Adapted from CS Document B Section B.2.3.6, Tables 9 and 10 (where further detail on assessment timing are available).

Additionally, the EAG noted that in response to clarification question B18, the company presented a Kaplan-Meier curve on time to non-oral feeding. The labelling of this figure was unclear, with the embedded heading on the figure saying it was time to sustained non-oral feeding and the separate heading on the clarification response saying it was time to oral

feeding. The EAG understood that this figure, shown below as Figure 2, is about time to non-oral feeding. The company has now confirmed that the EAG's understanding was correct.

Figure 2. Kaplan-Meier curves of time to sustained non-oral feeding for cPMP-treated and untreated patients (Full analysis set)

Source: Company clarification response, B18, Figure 5.

The curve for treated patients shows greater censoring than for untreated patients. cPMP administration was associated with longer time to sustained non-oral feeding, suggesting it slowed deterioration associated with MoCD Type A. However, non-oral feeding was still a common outcome.

Across the presentation of clinical effectiveness evidence, there were fluctuations in the available sample size across analyses. The EAG considered that the patient flow was not well explained and accounted for and that therefore there were uncertainties as to how the sample size for each analysis was reached. Furthermore, there were differences in the sample size used between the clinical and economic analyses. The EAG considers this to be in large part due to the use of different data cuts for the clinical and economic analyses. The survival analysis used to inform the economic model used the July 2019 data-cut, whereas the clinical effectiveness data used the October 2021 data-cut. The company said that the July 2019 data-cut is the latest one for which individual participant level data were available, however the EAG could not understand this rationale, as individual participant level data would be required to

present the results in the clinical effectiveness section. There was in general a lack of clarity in how the company presented information regarding sample size and data cuts used in different analyses.

The company responded that the use of older clinical data (July 2019 vs October 2021) for the survival analysis in the economic model compared to the clinical effectiveness section was because it did not have access to the underlying individual patient dataset for the more recent data. The CSRs and EMA submission contain the October 2021 data, however this could not be incorporated into the economic model without the individual patient data. The company clarified that the reason it did not have access to the underlying individual patient dataset for the updated clinical data was that its "statistics vendor did not provide these datasets", as provision of these datasets was not mandated for EMA submission. The EAG considered this to be unsatisfactory and thought that the company should request these datasets from its vendor so as to produce an economic model incorporating the more recent clinical data.

3.2.2.7. Critical appraisal of the design of the studies

The EAG agreed with the company that there are some concerns about the overall robustness of the evidence base for MoCD, including a sparse evidence base with most included studies in the company's SLR being case reports or case series and concerns about potential double-counting of individual patients given the low prevalence of MoCD and anonymous reporting, meaning that the same patient could feature in multiple studies undetected.

The company presents detailed critical appraisal of two cohort studies (Confer et al 2021[20] and Schwahn et al 2015[21]), one review (Schwahn et al 2021) and fifteen case reports and case series using JBI tools appropriate to the study methodology. These are shown in the CS Appendix D Section 4.3.

In response to a question from the EAG, the company clarified that the pivotal studies MCD-201,[18] MCD-202,[19] MCD-501[17] and MCD-502[1] have not been published separately. One of the included studies in the company's SLR[21] is an overlapping population to MCD-501[17] but is a different study, being prospective, while MCD-501 is retrospective. One conference abstract[20] presents an interim analysis from the integrated efficacy analysis, but there is as yet no publication presenting the final data cut as used in the company submission. The company present a critical appraisal of the published evidence rather than the final data cuts for their pivotal studies from the CS. Therefore, the company's risk of bias assessment was considered by the EAG to be of limited relevance to the decision problem.

The company's assessment of the Confer et al[20] abstract is shown below as – noting that this is not the final integrated efficacy analysis as presented in the CS.

Table 10. JBI Critical Appraisal Checklist for Cohort Studies for Confer et al (2021)

Risk of bias domains	Confer et al (2021)
1. Were the two groups similar and recruited from the same population?	Yes
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	No
5. Were strategies to deal with confounding factors stated?	No
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	No
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Unclear
10. Were strategies to address incomplete follow up utilized?	Unclear
11. Was appropriate statistical analysis used?	Not applicable
Overall bias	High

Source: Adapted from CS Appendix D, Section 4.3.1, Table 4.

The EAG agreed with the company's assessment that Confer et al[20] was likely to be at high risk of bias. The EAG considered it reasonable to assume that the overall bias portfolio is unlikely to be substantially different for the final data cut compared to the interim analysis. The EAG disagreed that 'appropriate statistical analysis' should be considered not applicable and considered that the company's assessment had not taken into account of the specifics regarding pooling.

3.2.3. Description and critique of the results of the studies

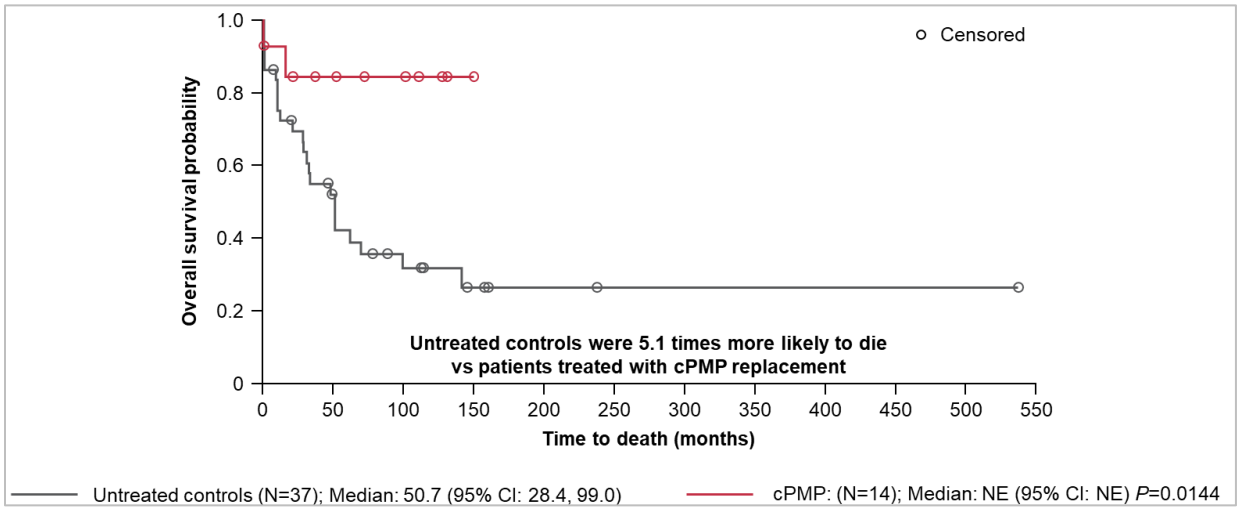
The company presented clinical effectiveness results from the integrated efficacy analyses rather than from the individual studies. Therefore, the same approach is taken here.

3.2.3.1. Clinical effectiveness results

Overall survival

A statistically significant improvement in OS was observed for people with MoCD Type A on cPMP treatment versus the untreated population in both the full analysis set (FAS) and genotype-matched analysis set (GMAS). Due to the low number of deaths during the period of observation in the cPMP group, median OS was not estimable in either analysis set. For the untreated population, median OS was 4.2 years in the FAS and 3.9 years in the GMAS. The rate of death in the untreated group was significantly higher than in the treated group, both in the FAS (HR 5.5, 95% CI 1.44, 21.04) and in the GMAS (HR 7.1, 95% CI not presented). The EAG considered the FAS to be the most relevant analysis set as it maximises available sample size. In the FAS, the survival probability at one year was 93% for the treated group and 75% for the untreated group. At two years, the survival probability was 86% for the treated group and 70% for the untreated group. At three years, the survival probability was 86% for the treated group and 55% for the untreated group. Kaplan-Meier OS curves comparing the treated and untreated groups in the FAS are shown below as Figure 3. No test of proportional hazards was presented, meaning there is uncertainty whether the Cox models provided a reliable estimate of treatment effectiveness.

Figure 3. Kaplan-Meier plot of OS for cPMP-treated people with MoCD and untreated controls (FAS, data cut-off 31 October 2021)



Source: CS Document B, Section 2.6.1, Figure 10. cPMP, cyclic pyranopterin monophosphate; NE, not estimable.

MoCD urinary biomarkers

MoCD urinary biomarker findings used the FAS. They were reported as group-specific mean values. No confidence intervals or tests of statistical significance were provided in the CS.

Mean urinary SSC levels normalised to creatinine were 136.3 µmol/mmol at baseline for untreated patients and 166.3 µmol/mmol for treated patients. After three months and at the final visit, mean levels had fallen to 12.3 µmol/mmol and 8.6 µmol/mmol in treated patients and risen to 159.6 µmol/mmol and 156.6 µmol/mmol in untreated patients respectively.

Mean urinary xanthine levels normalised to creatinine were 315.8 µmol/mmol at baseline for untreated patients and 241.8 µmol/mmol for treated patients. After three months and at the final visit, mean levels had fallen to 8.8 µmol/mmol and 17.9 µmol/mmol in treated patients and risen to 558.4 µmol/mmol and 338.2 µmol/mmol in untreated patients respectively.

Mean urinary uric acid levels normalised to creatinine were 99.1 µmol/mmol at baseline for untreated patients and 428.8 µmol/mmol for treated patients. It should be noted that unlike the other biomarkers, low values for uric acid are problematic. A value <100 µmol/mmol is in the clinically pathologic range. The interpretation of findings over time is challenging due to the marked difference in baselines, yet there was a mean increase of 77.6 µmol/mmol in treated patients and a mean reduction of -67.7 µmol/mmol in untreated controls to the last visit.

Feeding patterns

At the last recorded visit, 57% of treated patients and 30% of untreated patients were able to feed orally, with treated patients 7.8 times more likely to be able to feed orally. Median time to sustained non-oral feeding was 75 months for treated patients compared to 10.5 months for untreated patients. The FAS for treated patients was considered to comprise 14 people with early-onset MoCD. Oral feeding was significantly more frequent on treatment than in untreated controls in both the FAS (OR 7.8, 95% CI 1.38, 43.84) and the GMAS (OR 9.1, 95% CI 1.16, 72.39). An additional conditional logistic regression in the GMAS also showed a comparable result (HR 4.2, 95% CI not reported in the CS).

Growth parameters

Growth, as measured by body weight, body length, head circumference and BMI, was greater for treated patients compared to untreated controls. Median z-scores at the last assessment were: -0.34 (range -2.8, 2.5) and -0.63 (range -3.0, 2.8) for weight for treated patients and

untreated controls, respectively; -0.86 (range -7.1, 2.8) and -1.37 (range -4.6, 5.4), respectively, for height; and -0.70 (range -5.1, 3.0) and -1.91 (range -7.5, 4.3), respectively, for head circumference. This indicates that treated patients had growth that was closer to their age-matched peers than untreated control patients. No statistical test results were presented in the CS for growth parameter data.

The FAS for treated patients also comprised 14 people with early-onset MoCD for growth parameters. Results for growth parameters are shown in Table 11 below.

Table 11. Summary of first value and last assessment for weight, height, and head circumference z-scores (FAS and GMAS, MAA data cut-off 31st October 2020)

	Treated patients*	**Untreated controls**	
Parameter	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Baseline, n	14	37	19
Mean (SD)	-0.18 (0.880)	-0.28 (1.364)	-0.45 (1.538)
Last visit, n	14	37	19
Mean (SD)	-0.33 (1.237)	-0.70 (1.391)	-0.24 (1.555)
Baseline, n	12	33	16
Mean (SD)	-0.96 (2.724)	-0.44 (2.912)	-0.22 (3.630)
Last visit, n	13	33	16
Mean (SD)	-0.88 (2.394)	-1.05 (2.381)	-0.67 (2.738)
Baseline, n	13	36	19
Mean (SD)	0.56 (1.121)	-0.79 (2.862)	-1.58 (3.380)
Last visit, n	14	36	19
Mean (SD)	-0.52 (2.393)	-2.03 (2.783)	-2.33 (3.218)

Source: Based on CS Document B Section 2.6.4, Table 18. * FAS and GMAS.

Developmental assessments

At the last GMFCS assessment, a greater proportion of participants receiving cPMP were ambulatory (scoring Level 1) than untreated controls (44% vs 9%). However, this should be interpreted with caution due to baseline imbalances with a greater proportion of participants in the untreated group scoring indicating a greater degree of mobility impairment at baseline (82% in the untreated group scoring Level 5 indicating requiring wheelchair transportation vs 44% in the treated group).

Participants in the treated group had better scores at the last assessment on the Bayley test of development and the WPPSI test of cognitive function (as detailed in CS Table 20). These differences did not appear to be explained by baseline imbalances. By 12 months of age, three of the seven treated patients (43%) with data available were able to sit unassisted for 30 seconds, compared with three of the 27 untreated control patients (11%).

The FAS for treated patients for developmental assessments again consists of the 14 early onset patients. However, data were not available for all patients for all the developmental assessments, for example for GMFCS, data were only available for 10 treated patients and 14 untreated controls, and at the final assessment these numbers were nine and 11. Data were also available for the GMAS and results were similar. No statistical test results were presented in the CS for developmental assessments.

Neurological assessments including seizures

Ongoing seizures were common in both groups (50% of treated patients and 35% of untreated controls). More participants in the treated group (24%) had seizures resolved than the untreated control group (3%). Treated patients were considered more likely by the company than untreated controls to have seizures not present or resolved compared to controlled or continuing (FAS OR 1.216, 95% CI 0.337, 4.387; GMAS OR 1.461, 95 % CI 0.368, 5.808), although the EAG noted that the confidence intervals crossed the 1 indicating lack of statistical significance.

Across both groups, most participants had abnormal MRI imaging results. However, neurological functioning at the last visit was better for treated patients than untreated controls. Using data from the FAS, a lower percentage of patients receiving cPMP treatment had abnormal results at the last assessment for truncal tone (50.0% treated vs 89.2% untreated), appendicular tone (57.1% treated vs 94.6% untreated), and deep tendon reflexes (64.3% treated vs 81.1% untreated). No statistical test results were presented in the CS for these outcomes.

Health-related quality of life

The company did not include health-related quality of life assessment in its studies. As this is an ultra-rare condition and there have been no previous disease-modifying treatments, there are no pre-existing health-related quality of life data for MoCD (any type). Therefore, the company used health-related quality of life data from Dravet syndrome identified through a systematic review in order to generate utility values to inform the company's model. Data from a proxy condition may

increases uncertainty, since all conditions differ in their clinical features and resultant impact on health-related quality of life. Clinical advice to the EAG was that Dravet syndrome was a good match for MoCD in terms of its clinical characteristics, at least an 80-90% match, and there are more data available for Dravet due to its higher prevalence. The EAG noted that the company has modelled 50% of patients being on anti-seizure medication, whereas it would be expected that all people with Dravet syndrome would be on anti-seizure medication. However, clinical advice was that in both conditions, at least for early-onset MoCD, it is likely that almost all patients would be on anti-seizure medication and that the conditions would be very similar in this regard.

Subgroup analyses

There were no subgroup analyses in the company decision problem for this appraisal. As such, there are no economic subgroup analyses presented in the CS. Some clinical subgroup findings are presented in CS Document B Section 2.7, including on time of cPMP treatment initiation and gender. Results were presented in text rather than in tables and were generally not presented in much detail. Early initiation of treatment (within 14 days of birth) was not associated with survival outcomes, but was associated with greater likelihood of oral feeding (63.6% vs 0% for later initiation), improved head circumference z-scores (median 0.19 vs -2.52, IQR not reported), ambulatory status (57.1% vs 0%), being able to sit unassisted (85.7% vs 0%), seizures being not present, resolved or controlled (63.7% vs 0%), and having normal neurological examination results, including spontaneous movements (45.5% vs 0%), truncal tone (27.3% vs 0%) and deep tendon reflexes (45.5% vs 0%). However, there was no apparent difference for height or weight. There were no apparent differences in outcomes on cPMP treatment related to gender.

Adverse effects

Among the 15 participants who received cPMP treatment, overall patient-years of exposure were 83, with a median exposure of 5.4 years (range 6 days to 13.4 years). At the safety data cut-off of 31 October 2021, there were ten participants ongoing on fosdenopterin treatment (eight in study MCD-201[18] and two in study MCD-202[19]). All 11 participants in studies MCD-201 and MCD-202 (where fosdenopterin was administered) experienced treatment-emergent adverse events. There were treatment-related treatment-emergent adverse events in three participants in MCD-201 (37.5%) but none in MCD-202. Severe treatment-emergent adverse

events were encountered by 5 participants in MCD-201 (62.5%) and two participants in MCD-202 (66.7%), but these were not considered treatment-related (CS Document B Table 27).

A total of three deaths were reported across the four clinical studies, including two patients with MoCD Type A (study MCD-501[17]) who died while receiving rcPMP under named-patient-patient use from RSV pneumonia and necrotising enterocolitis, respectively, and one patient with MoCD Type B who died more than 2 years post-treatment of an unknown cause. The death due to necrotising enterocolitis was assessed as possibly related to treatment with rcPMP. This patient had a complicated medical course, receiving multiple concurrent treatments, and died at 6 days of age. No treatment-related deaths were observed in studies MCD-201[18] and MCD-202[19]. Further details on adverse event types can be found in the CS Section B.2.10.2.

3.3. Conclusions of the clinical effectiveness section

The company presented a clinical effectiveness SLR, which the EAG considered to be generally well conducted and well-reported. The clinical effectiveness results were presented in the form of an integrated efficacy analysis whereby the company pooled the results of three studies on cPMP (two were strictly on fosdenopterin and one was on a molecule with equivalent moieties, recombinant cPMP) and one natural history study on an untreated cohort. Outcomes in the companies studies were well-aligned to the NICE scope, with the exception of a lack of any data on health-related quality of life, which necessitated utility values from a proxy condition (Dravet syndrome) being used in the economic model. The integrated efficacy analysis presented clinical results in terms of: i) overall survival, ii) MoCD urinary biomarkers, iii) feeding patterns, iv) growth parameters and v) developmental assessments. Overall, the evidence showed a fairly consistent benefit of cPMP treatment over untreated controls. However, for some measures, there were concerns that baseline imbalances may at least in part explain the findings.

The EAG identified three key issues in the clinical effectiveness evidence base relating to: i) uncertainties related to non-randomised evidence and small sample size, ii) inconsistency of numbers included in the clinical inputs to the economic model and iii) health-related quality of life.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company carried out systematic literature reviews to identify prior cost-effectiveness analyses and evidence related to either cost and resource use or health-related quality of life of patients with MoCD Type A. Each of the three search strategies identified no studies. The EAG reviewed the search strategies and inclusion criteria used for the literature reviews and considered them all to be appropriate. This suggests that the absence of any literature related to MoCD Type A is a symptom of the rarity of the disease, rather than a fault in the approach to identifying evidence.

The company then conducted further systematic literature reviews to identify studies on the same topics, but this time in Dravet syndrome, which the company considers to be a proxy for MoCD Type A. A summary of the EAG's critique of the methods used in these literature reviews is provided in Table 12, Table 13 and Table 14.

Table 12. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence in Dravet syndrome

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G, sections 9.1-9.4	The searches were carried out in a good variety of sources. No subject headings were used for the main search terms for MoCD (Table 9, line 1) or for Dravet syndrome (Table 17, line 1) which is not best practice. Truncation and adjacency operators were not used, which would have expanded the search. This search was combined with a collection of terms relating to cost effectiveness; but it does not appear that a tested search filter has been used (such as those by SIGN[22] or CADTH[23]). It is possible that some relevant records may have been missed.
Inclusion criteria	Appendix G	The population within the PICO refers to MoCD, however given the search criteria this appears to be a reporting error. Besides this the inclusion criteria are appropriate.
Screening	Appendix G	Appropriate
Data extraction	Appendix G	Appropriate
QA of included studie	Appendix G	Quality assessment of cost-effectiveness evidence was conducted using the JBI Critical Appraisal Checklist for Economic Evaluations and is appropriate.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; JBI, Joanna Briggs Institute; QA, quality assessment

Table 13. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life in Dravet syndrome

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix H, sections 8.1-8.4	The searches were carried out in a good variety of sources. No subject headings were used for the main search terms for MoCD (Table 11, line 1) or for Dravet syndrome (Table 17, line 1) which is not best practice. Truncation and adjacency operators were not used, which would have expanded the search. This search was combined with a collection of terms relating to health-related quality of life; but it does not appear that a tested search filter has been used (such as those by SIGN[22] or CADTH[23]). It is possible that some relevant records may have been missed.
Inclusion criteria	Appendix H	Appropriate PICO with no restrictions applied to study age, location or language.
Screening	Appendix H	Appropriate
Data extraction	Appendix H	Appropriate
QA of included studies	Appendix H	Adaptation of the CASP checklist recommended in DSU TSD 9. It would have been preferable to use the CASP checklist directly for assessing HRQoL evidence, rather than using an adaptation of the checklist.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 14. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs in Dravet syndrome

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G, sections 9.1-9.4	The searches were carried out in a good variety of sources. No subject headings were used for the main search terms for MoCD (Table 9, line 1) or for Dravet syndrome (Table 17, line 1) which is not best practice. Truncation and adjacency operators were not used, which would have expanded the search. This search was combined with a collection of terms relating to cost effectiveness; but it does not appear that a tested search filter has been used (such as those by SIGN[22]

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		or CADTH[23]). It is possible that some relevant records may have been missed.
Inclusion criteria	Appendix G	The population within the PICO refers to MoCD, however given the search criteria this appears to be a reporting error. Besides this the inclusion criteria are appropriate.
Screening	Appendix G	Appropriate
Data extraction	Appendix G	Appropriate
QA of included studies	Appendix G	Cost and resource use evidence is assessed using a set of questions produced by Molinier et al.[24], on further investigation these are derived from the Drummond checklist, they provide an appropriate level of quality assessment.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

The searches identified four cost-effectiveness analyses with one in a UK setting. 11 studies related to health-related quality of life were identified, with six reporting health state utility values. 12 studies reporting either cost of managing Dravet syndrome or the healthcare utilisation of the disease were identified.

The value that systematic literature reviews in Dravet syndrome contribute to the appraisal of fosdenopterin as a treatment for MoCD Type A is uncertain and is dependent upon how appropriate Dravet syndrome is as a proxy for MoCD Type A. This is considered in greater detail in Section 3.2.3.1**.** However, if Dravet syndrome is considered a valid proxy for a MoCD Type A, then the searches appear to be methodologically robust and provide a good overview of the evidence base available to inform an economic analysis.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 15: NICE reference case checklist

Attribute	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The perspective of carer outcomes in addition to patients was relevant
Perspective on costs	NHS and PSS	No comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No comment

Attribute	Reference case	EAG comment on CS
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company's use of a lifetime horizon was appropriate. However, depending on the plausibility of survival extrapolations, a lifetime horizon of 100 may be excessive
Synthesis of evidence on health effects	Based on systematic review	The company conducted systematic reviews in MoCD Type A to obtain clinical data. Due to absence of HRQoL data from MoCD Type A, the company also conducted systematic reviews in Dravet syndrome
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs. The proxy Dravet syndrome study, which informed the utility values for some ages in the model, used the EQ-5D-5L
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	In the proxy Dravet syndrome study the EQ-5D-5L was completed by caregivers on the patients' behalf
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Index values were based on the UK value set
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No comment
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No comment
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The annual rate was equal for both costs and health effects. The EAG noted that the committee may wish to consider a 1.5% discount rate.

Abbreviations: EQ-5D, EuroQol 5 dimension; CS, company submission; eMIT, electronic Market Information Tool; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

Given the absence of any prior cost-effectiveness modelling work in MoCD Type A (Section 4.1) the company developed a *de novo* cohort-level model in Microsoft Excel®. The model was comprised of two health states, alive and dead. Patients were intended to move between health states every 4 weeks, although this was not correctly implemented in the model (see Section 6.1).

MoCD Type A is characterised by a shorter life expectancy and causes seizures, making feeding difficult and compromising mobility[25]. The model structure only explicitly captures differences between fosdenopterin and SOC in relation to life expectancy because, the company proposes, the primary benefit of fosdenopterin is improved survival. The cost implications of implementing nasogastric feeding to overcome feeding difficulties were captured in the alive health state. While the impacts of non-mortality symptoms of MoCD Type A on patient's health-related quality of life are captured implicitly by the utility value applied to SOC patients. The resolution of these symptoms by providing fosdenopterin then leads to an increase in utility. This means that the economic benefit of fosdenopterin to improving specific symptoms cannot be tested using the model in its current form.

The EAG is mindful that there is no conclusive evidence that any of the non-mortality symptoms are categorically resolved if treated with fosdenopterin. As a result, outcomes could differ depending on the symptoms a person is experiencing, and these differences would not be fully captured by the economic model. The EAG is concerned that the outcomes for people with MoCD Type A would be differentiated by their seizure history, but the model cannot reflect this. In the clinical analyses seizure outcomes are measured categorically with people recorded as, 'never had seizures,' 'had seizures but resolved', 'had seizures controlled with medication', or 'still having seizures regularly' at last visit. The point estimate of an odds ratio suggested that fosdenopterin improved seizure status, but this was not a statistically significant result. Crucially seizures still occur in both treatment groups, with varying proportions meeting each criterion, and this is not reflected in the model (beyond the cost of providing antiseizure medication for each treatment group).

4.2.3. Population

Per the final scope issued by NICE, the population relevant to this appraisal is defined as people with MoCD Type A[15]. The economic model developed to inform the company's submission is described by the company as reflecting *"all patients with MoCD Type A in England and Wales"* (CS, Section B.3.2.1, p.95). The company's base-case analysis reflects a population described in the model as the 'all patient set'. As an alternative analysis, the company's model includes a population described as 'early-onset patients'. The early-onset population makes use of the early-onset population of MCD-502[1] (N=33) instead of the FAS (N=37). MCD-502 is the natural history study, and so changing the population from 'all patient set' to 'early-onset patients' only impacts the SoC arm of the model.

For completeness, the EAG understands that the submitted model could generate two comparisons:

- **Base-case comparison:** N=12 patients from MCD-201,[18] MCD-202,[19] and MCD-501[17] for fosdenopterin; versus N=37 patients from MCD-502[1] for SoC ('all patient set').
- **Sensitivity analysis:** N=12 patients from MCD-201,[18] MCD-202,[19] and MCD-501[17] for fosdenopterin; versus N=33 patients from MCD-502[1] for SoC ('early-onset patients').

The EAG's critique of the clinical effectiveness evidence presented in this submission is provided in Section 3.2 of this report. Each of the individual studies used to inform the model were non-comparative studies, which was expected given the rarity of MoCD Type A. Acknowledging this, it is important to consider the comparability of the populations to ensure that a fair comparison is made between the treatment strategies being compared by the model.

Based on the EAG's understanding, people that were treated with fosdenopterin in the MCD-201,[18] MCD-202,[19] and MCD-501[17] studies and were captured in the analyses used to inform the economic model, would all be defined as 'early-onset' patients. This is because N=14 of the total N=15 treated patients were aged ≤ 28 days at onset of first MoCD symptoms, and data for the remaining late-onset patient did not appear to influence the economic model. This was also evident based on the population switch ('all patient set' versus 'early-onset patients') which only influenced the SoC arm of the model. The model was therefore not capable to reflecting the expected costs and outcomes for all people with MoCD Type A that could be treated with fosdenopterin – rather, it could only reflect outcomes for people with early-onset MoCD Type A.

For the SoC arm, as previously highlighted, there is an option to remove N=4 patients from the 'all patient set' to consider only those people defined as having early-onset MoCD Type A. Following consultation with the EAG's clinical expert, the EAG is aware of the important differences in outcomes for people who have early-onset versus late-onset MoCD Type A. The EAG understands that earlier onset of MoCD Type A symptoms is typically associated with increased disease severity, including increased mortality. In line with expectation, removing the N=4 late-onset patients from the MCD-502[1] study causes the modelled survival for the SoC to decrease (relative to the full population). However, the resultant modelled survival is greater than expected, based on advice received from the EAG's clinical expert (see Section 4.2.6 for further details regarding survival extrapolation).

In summary, the EAG believes that the economic evidence supporting fosdenopterin is only sufficient to make decisions related to people with early-onset MoCD Type A, which constitutes all of the patients in the MCD-201,[18] MCD-202,[19] and MCD-501[17] studies for whom data are used to populate the economic model. The model is not capable of generating estimates of cost-effectiveness for an all-comers population for both treatment arms, nor is it capable of evaluating a late-onset subgroup. Despite this, advice from the EAG's clinical expert was that the early-onset group represents the primary group of people that would be considered likely to derive benefit from fosdenopterin. The EAG's critique therefore focuses mostly on the early-onset subgroup.

4.2.4. Interventions and comparators

The intervention in the analysis was intravenously administered fosdenopterin, which is available in 9.5mg vials. The recommended dose for people aged 1+ years is 0.9 mg/kg administered once daily. For people under one year of age, a titration schedule is followed with the objective of reaching the 0.9 mg/kg target dose by month three. The schedule differs for preterm and full-term neonates, and both schedules are presented in Table 16. The cost-effectiveness modelling assumed people start receiving fosdenopterin at birth, and an even split between preterm and full-term neonates. The former assumption was discussed with the EAG's clinical expert and is considered to be reasonable given how closely positive long-term outcomes and early diagnosis are expected to be linked. This is also related to the EAG's position on the population (Section 4.2.3) that the evidence provided for fosdenopterin is more aligned with an early-onset MoCD Type A population than with MoCD Type A overall.

Table 16: Starting dose and titration schedule of fosdenopterin for people less than one year of age by gestational age

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

Key: kg, kilogram; mg, milligram.

The company did not provide specific rationale for estimating the dosage assuming an even split of preterm and full-term neonates. The mean and median gestational ages at baseline in each of the trials were >37 weeks but each trial included people that would be classified as

preterm. However, the assumption is inconsequential to cost-effectiveness results as full vial wastage is assumed and therefore one full vial a day is required to cover either titration schedule.

The symptom managing treatments modelled in the SOC arm included anti-seizure medication and nasogastric feeding. The company only modelled anti-seizure medication use in [redacted] of SOC patients and [redacted] of fosdenopterin patients. This was out of step with the experience of the EAG's clinical expert, who believed all people managed with SOC would be receiving anti-seizure medication, but they only had first-hand experience with early-onset MoCD Type A and noted that the management of late-onset MoCD Type A may differ.

4.2.4.1. Time on treatment

The model did not include discontinuation in the base-case analysis. Given the severity of MoCD Type A, people are not expected to discontinue treatment unless their prognosis is extremely poor. This is reflected in the trials investigating fosdenopterin, with the only discontinuations being associated with deaths. The EAG's clinical expert had a similar expectation for the duration of treatment on fosdenopterin, that people would remain on treatment long-term unless they were not responding to treatment, at which point prognosis would be aligned with the description provided by the company. In principle, the EAG agrees with the assumption implemented by the company with relation to treatment discontinuation. Fosdenopterin directly replaces the cPMP that a person is unable to produce, therefore discontinuing treatment with fosdenopterin to start treatments that can only manage the symptoms of MoCD Type A seems unlikely.

The EAG reflected on whether the model accurately reflects the identification of people who do not respond to fosdenopterin. The EAG's clinical expert highlighted that there could be instances where people with early-onset MoCD Type A do not respond to treatment, and as a result would be discontinued. These people would then have the same prognosis as those who receive SOC. As discussed in more detail in Section 4.2.6, the EAG's clinical expert believed the prognosis of early-onset MoCD Type A people to be poorer than suggested by the company, with survival of approximately 3 years. Given this, the EAG believes that the non-responders are implicitly captured within the trial evidence, with the people who did not respond to treatment being those who died in the study. The remaining people must respond to treatment to achieve the survival outcomes seen in MCD-201,[18] MCD-202[19] and MCD-501.[17]

The main treatments provided as part of SOC to provide symptom management included anti-seizure medication and nasogastric feeding. The company did not model any discontinuation of anti-seizure medication, with the cost of treatment being applied to a constant proportion of people managed with SOC. This seems logical, but the EAG's clinical expert believed it may be possible for some fosdenopterin patients to come off anti-seizure medication in the longer-term.

The company modelled changing levels of nasogastric feeding overtime in its model, although the assumptions the company states in its submission, the evidence it provides to support these assumptions, and what is ultimately modelled all contradict one another. In its initial base case, the company states that in year one 42% of fosdenopterin patients and 67% of SOC patients feed non-orally, and then assumes that from year two onwards the fosdenopterin proportion reduces to 0% while the SOC arm remains the same. This was not initially justified in the CS, but supportive evidence was provided during the clarification stage (question B18). The company described how the need for nasogastric feeding is a result of irreversible developmental delays caused by a build-up of sulphites in the brain, the EAG's clinical expert agreed that brain damage caused by sulphites would be irreversible. The EAG's clinical expert elaborated further, noting that the provision of fosdenopterin prior to this build-up could result in a person avoiding the need for nasogastric feeding. The company then presented a supportive plot (Figure 4) that it labelled as "time to oral feeding", but, based on the labelling in the figure itself, is in fact time to sustained non-oral feeding.

Figure 4: Time to non-oral feeding (Clarification response B18)

The EAG's interpretation of the evidence related to nasogastric feeding differs to the company's. The impact of MoCD Type A [redacted] the concept of all people treated with fosdenopterin being able to feed independently [redacted]. Any damage caused to the brain by sulphite build up would be irreversible, and therefore, any patients that required nasogastric feeding in [redacted]. The figure presented in response to clarification question B18 also suggests that the proportion of patients that will be able to orally feed [redacted] over time. This [redacted] appears to occur at [redacted] for people receiving fosdenopterin versus SOC, but the figure [redacted] non-oral feeding [redacted] [redacted] fosdenopterin as the company suggests.

[redacted] the company's position regarding the benefit of fosdenopterin related to feeding difficulties for MoCD Type A, and the evidence the company provides, [redacted] [redacted] by errors in the company's modelling approach. The company applied the year two non-oral feeding percentages in year one and then applied the year one percentages in year two onwards. The EAG believes that this error may in fact result in modelling that [redacted] what the company described in its submission. The EAG revised this area of the model, details of which are described in Section 6.2.1.

4.2.5. Perspective, time horizon and discounting

The perspective of the analysis presented by the company was that of the NHS and PSS on costs, and patients and carers on outcomes. This overall perspective, including the addition of carers for outcomes, was in line with Section 4.3.17 of the NICE reference case, which states that *"evaluations should consider all health effects for patients, and, when relevant, carers. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's health-related quality of life and how the technology affects carers"*. After consultation with its clinical expert, the EAG agreed that capturing the health effects of carers was relevant to this submission, but the EAG had concerns about the strength of evidence provided and assumptions made by the company for carer outcomes. This is covered in more detail in Section 4.2.7.3.

The company discounted costs and health outcomes at 3.5% per annum. The EAG noted that while a discount rate of 3.5% per annum is recommended in the NICE reference case as standard, there may be a case for this appraisal for use of non-reference-case discounting of 1.5% per annum. Section 4.5.3 of the NICE reference case states that the 1.5% discount rate for costs and health effects may be considered if:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

The EAG considered that the first criterion was met for this indication, and that the latter two criteria may also be met and appear to be put forward by the company. The EAG therefore noted that the committee may wish to consider the use of 1.5% per annum discount rates for costs and outcomes.

The model adopted a lifetime horizon with a maximum age of 100 years. In the base case, people enter the company's model at an age of zero (i.e., at diagnosis shortly after birth), and fosdenopterin treatment is expected to also start immediately after birth. The EAG agreed that the use of a lifetime horizon was appropriate. However, depending on the plausibility of survival extrapolations, a lifetime horizon of 100 years may be excessive, as is discussed further in Section 4.2.6.

4.2.6. Treatment effectiveness and extrapolation

Given the nature of the company's model, a two-state model wherein only one transition (from alive to dead) can occur, the outcomes of the model are almost entirely dependent upon the extrapolations of overall survival data. The model includes a small number of other clinical inputs to inform resource use and tolerability, but given the severity of MoCD Type A and the costs associated with fosdenopterin, these have limited impact on model results.

The company conducted survival analysis on the July 2019 data-cut, which was the latest data-cut with individual patient level data available, though it is unclear to the EAG why the data informing the later October 2021 data-cut (see Figure 10 of the CS) could not be used. The EAG digitized the data presented in this figure, the Kaplan-Meier (KM) estimate for the fosdenopterin arm ends at a slightly higher percentage (84%) than it did in the July 2019 data-cut (81%), while the SOC OS was lower (26% versus 29%). Given the differences were minor, and are therefore unlikely to significantly impact economic results, the EAG did not fit parametric survival models to the re-created data cut. The fosdenopterin arm is constructed by naïvely pooling data from MCD-501,[17] MCD-201[18] and MCD-202[19] to create a population with 12 patients who have been treated with fosdenopterin or rcPMP. A KM estimate comparing the overall survival of the fosdenopterin arm and SOC arm can be seen in Figure 15 of the CS. For the SOC arm the company presented survival data from a natural history study of 37 patients with MoCD Type A. All comparative survival analysis was conducted naïvely, with no adjustments made to account for potential differences between the populations.

The EAG recognises that it would have been implausible to effectively implement any adjustment methods given the size of the evidence base. Although justifiable, the approach is inherently subject to a risk of bias in the resulting comparisons, and the EAG cannot determine which arm this bias appears to favour. Consequently, the EAG advises caution when interpreting the results of this naïve comparison.

The pooled data for the fosdenopterin arm provided more than 100 months (~8.3 years) of follow-up, with the last event occurring at 15.9 months (~1.3 years). The SOC arm includes more than 500 months (~41.6 years) worth of follow-up, however there were only 2 patients still at risk beyond 200 months (~16.7 years) and one beyond 250 months (~20.8 years). Overall, 24 deaths were observed in the SOC arm with the last event occurring at 141.1 months (~11.7 years).

The company also conducted an analysis focusing solely on people with early-onset MoCD Type A. This did not affect the analysis conducted on the fosdenopterin arm as all of the patients in the three trials informing the survival analysis used in the model were categorised as early-onset MoCD Type A. However, restricting the model to focus only on early-onset patients reduced the sample size of the MCD-502 study (i.e., the study for the SOC arm) by four patients from N = 37 to N = 33. The company presented a scenario using this population but did not describe the preferred parametric survival model fitted to this dataset.

As detailed in Section 4.2.3, following discussions with its clinical expert, the EAG considered that it was more appropriate to consider the role of fosdenopterin for treating people with early-onset MoCD Type A only, for two key reasons:

- First, the outcomes for people with early-onset MoCD Type A can differ significantly to those with late-onset disease, and
- Second, the trials providing evidence for the effectiveness of fosdenopterin only included people with early-onset MoCD Type A

The EAG expected that the inclusion of late-onset patients in the SOC analysis resulted in over-estimated survival outcomes that are not reflective of those that would have been achieved by the fosdenopterin patients, if they had not received the intervention. The EAG conducted an alternative analysis using the early-onset population, which is described further in Section 6.

Parametric survival models were fitted to each arm to estimate long-term survival probabilities. Models were fitted to each arm separately, and a jointly fitted model was also fitted to all of the data with a covariate to capture the effect of fosdenopterin. The company fitted the models following the guidance laid out in NICE TSD 14.[26] In its initial submission, the company provided separate and jointly-fitted models using the six distributions recommended in NICE TSD 14 (exponential, generalized gamma, Gompertz, log-logistic, log-normal and Weibull) along with the two-parameter gamma model. The company removed the generalized gamma during the clarification stage citing technical difficulties actioning this distribution in the model.

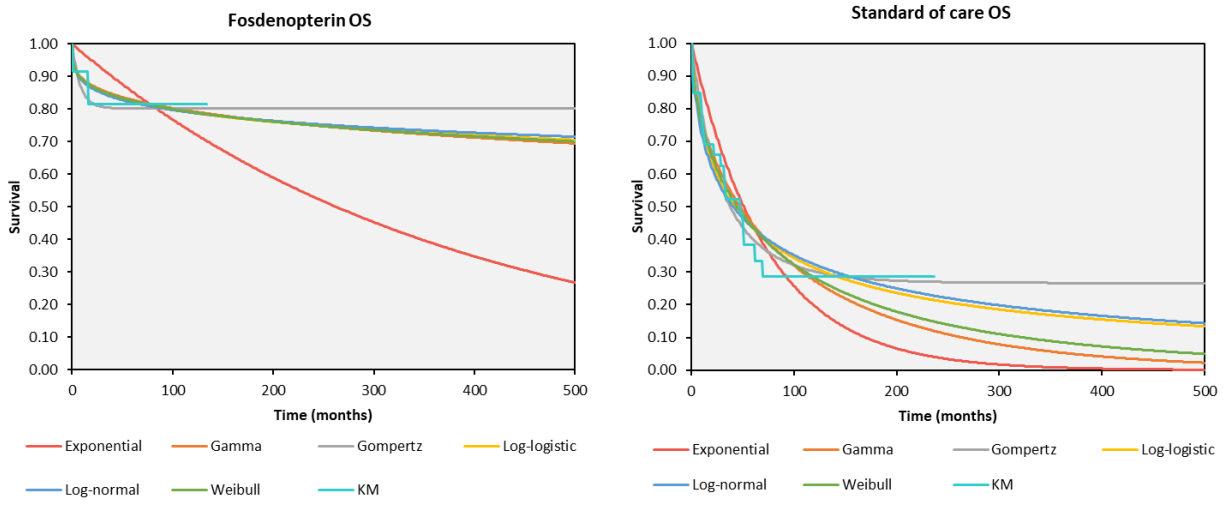
For the jointly-fitted model the company stated that the proportional hazards (PH) assumption was supported by observed data from the clinical trials. However, the EAG notes that supportive evidence such as the log-cumulative hazard plot provided at clarification stage provides inconclusive evidence for the PH assumption. The company also highlights that evidence of a

constant treatment effect during the observed period does not mean that the PH assumption can be assumed to be maintained over a lifetime horizon.

In its base-case analysis, the company used separately fitted models, with a log-logistic model used for the fosdenopterin arm and an exponential model used for the SOC arm. All of the separately fitted models are presented in Figure 5.

The models for the SOC arm are fitted to the early-onset data, as this is the dataset preferred by the EAG, however the early-onset KM plot was not available, so it is plotted against the overall population. Following discussions with its clinical expert, the EAG believes that all of the extrapolations may be optimistic compared to early onset patients in clincial practice. The company did not provide any clear justification for its base-case choice of exponential, other than it being "*considered the most plausible scenario*". This was contrary to the documentation of the company's clinical validation meeting, where the expert suggested the exponential model was the only model that was not "*plausible and reflective of long-term outcomes*", however the company has flagged that this was incorrectly reported in their appendix. The expert in fact confirmed that all the parametric survival models fitted to the SOC survival data were appropriate extrapolations. Given these points, the EAG agreed with the use of the exponential model for the SOC given it provides the most pesimistic estimate, despite its poor visual fit (as seen in Figure 5) and the extent of uncertainty in this estimate.

Figure 5: Separately fitted parametric survival models



Deciding on the best fitting model for the fosdenopterin arm is dependent on expectations for long-term outcomes that are inherently subject to substantial uncertainty. The last event occurs

at approximately 16 months after which there is approximately 7 years of event-free follow-up, but the tail of the KM estimate has few patients at risk. The company used a log-logistic model in its base case, which suggests a low rate of events beyond the observed period. This is a possible scenario, but given the uncertainty the EAG believes that the true OS could be realistically be anywhere between the company's prefered log-logistic and the exponential model fitted to the SOC arm.

The nature of treatment with fosdenopterin in terms of its impact on survival appears to be potentially curative (with respect to disease-specific mortality). This is somewhat evidenced in the data provided by the company, which shows a marked improvement in survival compared with the SOC arm. As a result, the parametric survival model extrapolations have what is commonly termed 'long tails' (i.e., a proportion of people that live for a long time with a reduced risk of death, compared to those people that die shortly after initiation of treatment) and general-population mortality data has a notable influence on model outcomes.

In its review, the EAG identified several errors in the company's modelling of general-population mortality, including:

- General population mortality was applied based on a probability for six months in each four-week model cycle (i.e., mortality risk was around 6x the value that would be expected)
- General population mortality was applied in the company's model in addition to disease-related mortality (i.e., there was a potential 'double-counting' of overall mortality risk)
- General population mortality was assumed to comprise of a fixed split of male and female patients based on the mean percentage of females across MCD-501,[17] MCD-201[18] and MCD-202[19]. Male life expectancy is generally shorter (compared with females), *ceteris paribus*, therefore the split is expected to change over time

These are addressed in Section 6.1 of this report.

4.2.7. Health-related quality of life

No health-related quality of life (HRQoL) data were collected in any of the clinical trials in MoCD Type A used by the company to inform its model. In addition, the HRQoL SLR performed by the company identified no health state utility values specifically for MoCD Type A. For critique of the methods of this SLR see section 4.1.

4.2.7.1. Impact of health state

The company model comprised of two health states for people with MoCD Type A: 'alive' and 'dead'. Utility for the 'dead' state was assumed to be 0. However, rather than specifying a single utility value for the 'alive' state, the company's model allowed utility values to vary over time based on two factors: (i) treatment assignment, and (ii) age (i.e., time since initiation of treatment, since all patients were assumed to enter the model at age 0 years).

4.2.7.2. Impact of treatment

As noted above, utility values for the 'alive' state of the company's model were contingent upon age and treatment assignment in the base case, as well as the occurrence of adverse events (AEs) in a scenario analysis. Treatment assignment impacted patients' utility through differing assumptions about age-based utility and AE utility decrements between the two arms.

Age-based utility

In the absence of HRQoL data specifically for MoCD Type A, the company identified data via a proxy SLR in Dravet syndrome, which identified 15 studies. Clinical input to the company confirmed Dravet syndrome as a reasonable proxy to infer quality of life. The EAG considered that, as with other areas of the company submission where Dravet syndrome is used as a proxy for MoCD Type A, this was an appropriate method given the absence of data specifically for MoCD Type A, though the use of any proxy introduces an additional layer of uncertainty. For the EAG critique of the methods of the Dravet syndrome HRQoL SLR see section 3.2.3.1 .

Of the selected studies, the company selected a pan-European study by Lagae *et al.* (2018)[27] reporting EQ-5D-5L in 584 patients because it was relatively recent, had a large sample size and collected EQ-5D from a range of patient ages. The EAG agreed that the Lagae *et al.* (2018)[27] paper was an appropriate source for Dravet syndrome HRQoL data. The utility values obtained from this study, which were used to inform some of the company's base case age-based utility values, are reproduced in Table **17**.

Table 17**. Reproduction of CS Table 16 - Utility values used in the model**

Age	Reported EQ-5D-5L
Infants (<2 years)	0.33
Preschool (2-5 years)	0.46
Middle childhood (6-11 years)	0.43
Adolescent (12-17 years)	0.43
Adult (18+ years)	0.34

The EAG noted that the utility values from Table 36 of the company submission were not used directly in the company's model. The company made assumptions about differences across arms and extrapolations beyond 18 years for age-based utility values.

For the SoC arm, the company claimed that the Lagae *et al.* (2018)[27] values were used up the age of 18, after which the Lagae *et al.* (2018) values were set to decline at a rate proportional to the general population utility decline. General population values were sourced from Ara and Brazier[28]. Under this assumption, the utility value at age 18 should have been 0.34, after which it would decline with age. However, the company model took the Lagae *et al.* (2018) values up to the age of 17 and following that the adolescent value of 0.43 was maintained. Additionally, the decline proportional to the general population was applied from age 18 rather than after 18. These values used by the company are presented for the ages 0 to 20 in **Error! Reference source not found.**.

For the fosdenopterin arm, the company used the Lagae *et al.* (2018)[27] value for the first year of life, after which patient utility values were assumed to be equal to the general population. This assumption was based on clinical input to the company suggesting early treatment with fosdenopterin would result in utility values comparable to the general population in the long term. The company justified use of this assumption by the absence of clear utility estimates in MoCD Type A. The company provided a scenario with fosdenopterin patient utility set to 50% of the general population following the first year, this led to an increase in the ICER by [redacted] (Section 5.2.3). The resulting utility values used by the company are presented for the ages 0 to 20 in Table 18.

Table 18. Age-based utility values used in the company model base case, ages 0 to 20

Age	SoC		Fosdenopterin	
	Value	**Source**	**Value**	**Source**
0	0.330	Lagae *et al.* (2018)[27]	0.330	Lagae *et al.*, (2018)[27]
1	0.330		0.965	General population values
2	0.460		0.965	
3	0.460		0.965	
4	0.460		0.964	
5	0.460		0.963	
6	0.430		0.963	
7	0.430		0.962	
8	0.430		0.961	
9	0.430		0.961	
10	0.430		0.960	
11	0.430		0.959	
12	0.430		0.958	
13	0.430		0.957	
14	0.430		0.955	
15	0.430		0.954	
16	0.430		0.953	
17	0.430		0.952	
18	0.429	Lagae *et al.*, (2018)[27] 12-17 value with decline proportional to general population	0.950	
19	0.429		0.949	
20	0.428		0.947	
…	Continued decline		Continued decline	

The EAG noted that the methods and assumptions which led to using Lagae *et al.* (2018)[27] values as a proxy for age-based utility values for patients in the model were broadly acceptable. However, there were inconsistencies between the company's description of methods in its submission and the company's model. The EAG noted that the company's base case approach, contrary to the description in the submission, omitted the 18+ utility value from Lagae *et al.* (2018) and instead assumed that the adolescent utility value was maintained into adulthood. The EAG agreed with the approach to assuming decline in utility values following 18 years of age proportional to the general population decline but preferred the use of the adult utility value reported in using Lagae *et al.* (2018). The use of the adult utility value rather than the

adolescent value from Lagae *et al.* (2018) was explored by the EAG in scenario analyses (Section 6).

The EAG had reservations about the appropriateness of the company's assumptions for patient utility in the fosdenopterin arm. Based on clinical input to both the EAG and the company, the EAG believed that Dravet syndrome potentially represented an upper bound for patient health-related quality of life for MoCD Type A for those receiving current standard of care (based on some differences in burden of disease for MoCD Type A versus Dravet syndrome). The EAG considered that it was possible that people with MoCD Type A receiving fosdenopterin *may* report higher HRQoL outcomes that those for Dravet syndrome reported in Lagae *et al.* (2018),[27] and that based on the results of the clinical trials for MoCD Type A it was reasonable to assume that patients in the fosdenopterin arm had a better quality of life than those in the SoC arm. However, the EAG noted that no clinical evidence submitted by the company indicated that MoCD Type A patients had outcomes in line with the general population at any time point. Clinical input to the EAG also suggested that MoCD Type A patients on fosdenopterin would only be expected to have a quality of life equal to general population estimates under very specific circumstances (diagnosis and treatment initiation in the first days of life and complete response to treatment). The EAG therefore considered it likely inappropriate to assume general population utility for all people treated with fosdenopterin in the model after 1 year.

Adverse event utility decrements

Treatment assignment also impacted utility in a scenario in the company's model through slightly different AE utility decrement assumptions based on treatment. The disutility values for AEs were claimed to be assumed as an annual decrement and were sourced by the company from Sullivan et al.[29]. The company used the same approach as for AE costs where, since AE rates were not available for the SoC arm, AE rates for the fosdenopterin arm were applied to both arms with a correction for AEs related specifically to fosdenopterin. This meant that the AE decrement for 'Injury, poisoning, procedural complications' and 'product issues' were omitted from the SoC arm due to being directly related to the administration of fosdenopterin. The company's approach is summarized in Table 19 and led to a total annual decrement value of -0.0041 for the fosdenopterin arm and -0.0036 for the SoC arm.

The EAG noted that the company's approach to estimating AE rates across arms was appropriate given the availability of data and agreed with the use of the Sullivan et al[29] source.

However, the EAG believed that the AE disutility for 'General disorders and administration site condition' should also have been omitted from the SoC arm due to its relevance to fosdenopterin treatment specifically. The EAG noted that, due to the low proportions assumed to experience AEs, this assumption had a small impact on the SoC decrement of reducing it to -0.0035. The EAG also noted that the company mistakenly applied the annual utility decrement directly each cycle rather than adjusting the decrement to a per cycle value. This was corrected by the EAG. The utility decrement values and proportions where these applied for each arm are summarised in Table 19.

The EAG noted that the company did not justify the exclusion of AE utility decrements from the base case analysis. The EAG found this an acceptable approach given that patient utility values were unlikely to be significantly influenced by AE experience.

Table 19. Adverse event decrements used by the company

Adverse event	Utility decrement	Description	Fodenopterin proportion	SoC proportion
General disorders and administration site condition	-0.0024	Other inflammatory condition of the skin	2.8%	2.8%
Infections and infestations	-0.0024	Other inflammatory condition of the skin	2.8%	2.8%
Gastrointestinal disorders	-0.0512	Gastrointestinal disorders	1.7%	1.7%
Skin and subcutaneous tissue disorders	-0.0006	Other skin disorders	1.7%	1.7%
Respiratory, thoracic and mediastinal	-0.0336	Asthma	1.4%	1.4%
Injury, poisoning, procedural complications	-0.0512	Gastrointestinal disorders	1.1%	0.0%
Product issues	-0.0024	Other inflammatory condition of the skin	0.2%	0.0%
Eye disorders	-0.0092	Other eye disorders	0.2%	0.2%
Metabolism and nutrition disorders	-0.0839	Nutritional disorders	0.6%	0.6%
Nervous system disorders	-0.0695	Other nervous system disorder	0.6%	0.6%

Adverse event	Utility decrement	Description	Fodenopterin proportion	SoC proportion
Psychiatric disorders	-0.1009	Other mental conditions	0.5%	0.5%
Surgical and medical procedures	-0.0024	Other inflammatory condition of the skin	0.5%	0.5%
Vascular disorders	-0.0531	Other circulatory disease	0.3%	0.3%
Cardiac disorders	-0.0246	Cardiac dysrhythmias	0.3%	0.3%
Ear and labyrinth disorders	-0.0103	Other ear and sense organ disorders	0.3%	0.3%
Musculoskeletal and connective tissue disorders	-0.0630	Other connective tissue disease	0.3%	0.3%
Hepatobiliary disorders	-0.0581	Hepatitis	0.1%	0.1%
Congenital, familial and genetic disorders	-0.0048	Other congenital anomalies	0.1%	0.1%
Immune system disorders	-0.0559	HIV infections	0.1%	0.1%
Neoplasms benign, malignant and unspecified (including cysts and polyps	-0.0086	Malignant neoplasm without specification	0.1%	0.1%

Abbreviations: SoC, standard of care.

4.2.7.3. Impact on carer health-related quality of life

In addition to the HRQoL of patients, the company modelled the caregiver burden in the model base-case. The company used a caregiver disutility of -0.14 which was taken from submission TA254[30] in multiple sclerosis and corresponded to the most severe health state requiring 14.8 hours of care per day. The company provided a scenario analysis with a smaller disutility of -0.05 corresponding to 5.6 hours of care per day. The company assumed that 1.8 caregivers would be required for the SoC arm, in line with TA808,[31] and assumed 1 caregiver for the fodenopterin arm due to the "*reduced need for caregiving when patients are adequately treated*". It was assumed that people with MoCD Type A receiving SoC would require support from caregivers for life, whereas burden on caregivers of fosdenopterin patients would cease after 5 years. The company justified these assumptions based on SoC not being expected to reduce the severity of MoCD Type A and fosdenopterin being expected to remove caregiver burden "*once treatment is initiated*".

The company calculated the utility of caregivers by taking the average new parent age in England and Wales in 2021 (33.7 for men, 30.9 for women giving 32.3 average) applied to Ara and Brazier[28] to obtain general population utility values, then applied the assumed disutilities.

The company only provided a brief justification for including caregiver burden but following advice from the EAG's clinical expert and considering the severity of MoCD Type A, the EAG agreed that caregiver utility was relevant to this decision problem. While the company did not detail the process of choosing TA254 as a proxy for caregiver disutility, the EAG noted that its clinical expert supported the expectation that full time care would be required for MoCD Type A patients, and that this care often represents and significant mental and physical toll for care givers. The EAG therefore agreed with the company's choice to include carer outcomes.

The EAG's main concern with the company's approach to caregiver utility was regarding the assumptions about the number of required caregivers and duration of care. The EAG believed that full time care was an appropriate assumption for the duration of a patient's life if they were receiving SOC. Clinical advice to the EAG suggested that one carer would be required, with another carer ideally trained as a precaution but both would not necessarily be required to provide full time care. However, given that the EAG's clinician also agreed that Dravet syndrome was a good proxy for MoCD Type A, the EAG accepted that aligning the number of carers with previous appraisals in Dravet syndrome was understandable. The value of 1.8 carers from TA808[31] was chosen to match the previous appraisal TA614,[32] which took the value from a large pan-European DISCUSS survey that found that 78% of caregivers were living in a household with more than one adult.[27] The EAG noted that this finding does not necessarily suggest that all adults in a household are caregivers, but accepted that the value of 1.8 carers was in line with previous appraisals for a similar condition.

The EAG also believed that the assumption that patients treated with fosdenopterin would no longer require a parent as a carer from the age of 5 was implausible based on expected patient outcomes and the administration process of fosdenopterin. The company claimed that all care would be institutionalised once a patient was able to enter the education system. The company also assumed that none of the care requirements of SOC patients were institutionalised in the same way in current practice and that they required full care for life. Clinical input to the EAG and the description offered by the company detailed the daily process of administering fosdenopterin as involving reconstitution in sterile water of multiple vials from a medical grade freezer, dose calculation based on body weight and intravenous injection. The EAG did not

believe that a 5-year-old could perform this procedure independently, or that it would be conducted at the patient's school, therefore they would require the support of a carer. The EAG also believed that expected patient outcomes while on fosdenopterin treatment presented in the company's submission demonstrated a continued requirement for care despite treatment with fosdenopterin. The EAG noted that many fosdenopterin patients at the end of trial follow up still experienced a seizure burden, had difficulty feeding and required transportation in a wheelchair. These care requirements would not be isolated to the time that patients were at school and would likely need care for the remainder of the day. The EAG found no evidence that a fosdenopterin patient would immediately have their care requirement reduced from 14.8 hours to 0 at the age of 5 years.

Clinical input to the EAG suggested that in theory an older patient with a best case fosdenopterin treatment response may be able to self-administer fosdenopterin in the future, but the EAG believed that this would be the case only for some patients and it is uncertain at what age this would be possible. The EAG believed that the average person with MoCD Type A on fosdenopterin would still require some level of carer support, although this may be reduced versus SOC. Alternative scenarios to those provided by the company were explored in Section 6.2.

The EAG noted some errors in the company's calculation of carer HRQoL values in the model.

- The company did not account for patient survival when deriving the disutility for carers, meaning carers were experiencing a decrement after the patient had died
- The company double counted caregiver disutility, applying it once to the patient QALYs and once to the utility of caregivers, which is tracked separately in the model
- The SoC number of carers was applied to the fosdenopterin arm in the model when applying the bereavement disutility to carers
- The outcomes were discounted using the time for the previous cycle

The company applied the percentage of caregivers alive twice for the bereavement utility decrement

The EAG corrected these errors in its revised model, as described in Section 6.1.

4.2.8. Resources and costs

4.2.8.1. Drug and administration costs

Intervention costs

The acquisition cost of fosdenopterin provided by the company was £1,206 per 9.5mg vial, with a simple patient access scheme (PAS) of [redacted] applied. Vial wastage was assumed which aligned with storage recommendations in the SmPC.[14] Dose administration costs in the company's base case depended on the assumed bodyweight of patients and on assumptions about administration setting.

The company assumed that patient weight in the model was set to the [redacted] percentile of the general population and justified this in the CS based on analysis of the patient-level data which demonstrated that *"patients with MoCD Type A do not achieve normal weight due to difficulty feeding"*. Post-submission, the Company amended their position as they believe this initial statement did not fully capture the comprehensive clinical context surrounding why patients with MoCD Type A fail to attain a normal weight. The EAG agreed that patients from the company's trials did not achieve normal weight during the trial period but disagreed that the trial data justified a [redacted] percentile patient weight assumption for the entire model time horizon.

Table 18 of the 'Growth Parameters' section of the company's submission contained summaries of weight z-scores for the treated and untreated groups at baseline and last visit. At last visit, the median z-score for the treated group was -0.34 and for the untreated group was -0.63. World Health Organisation (WHO) weight-for-age charts, which the company used in their model to source [redacted] percentile weight values up to 3 years, show that a z-score of -1 corresponds very closely (always within 100g for each month) to the 15th percentile weight[33]. Given that the z-scores from the trial data were between -1 and 0 the EAG considered 15th percentile weight to be a conservative lower bound for an appropriate weight assumption and 25th percentile patient weight to be the most appropriate.

Following the end of the company's use of the WHO weight-for-age tables at 3 years, the company switched to estimating [redacted] percentile weights based on alternative sources. The company confirmed at clarification that the percentage difference between the percentiles from the WHO tables at 60 months were calculated. The company then applied these percentage differences to mean weights from the Royal College of Paediatrics and Child Health UK-WHO growth charts 2-18 years for the ages of 4-15 years[34] and the Health Survey for England (HSE)

2021 Overweight and Obesity tables (although using 2019 values) for age 16 and onwards[35]. For all age ranges the company averaged weight across males and females according to the proportions from the clinical data. The EAG noted the following points regarding this approach:

- The 2021 values for HSE mean weights were available to the company, yet no justification for selecting 2019 values was given.
- The company did not provide justification for only using the WHO data up to the age of 3 rather than the full data up to the age of 5. The EAG noted that this approach did not happen to differ significantly with using the full WHO data, as WHO weights for ages 4 and 5 were 13.2kg and 14.6kg compared to the 12.9kg and 14.8kg used by the company. These differences only had a small impact on costs through SoC costs, as the weight threshold for requiring an additional vial of fosdenopterin was already reached at weight of 10.5kg.
- The company's approach assumed that the percentage differences at 5 years between weight percentiles were applicable at all future ages. The EAG noted that this assumption was not justified by the company but found the assumption acceptable.
- The company's approach assumed that the below average weights from the trial would be retained for the lifetime of patients in the model. The EAG believed that this assumption was inconsistent with the company's base case assumptions around patient quality of life for the fosdenopterin arm, especially under the assumption of [redacted] percentile weight. The EAG believed that maintaining a 25th percentile weight for the time horizon of the model may be more appropriate (though there is no direct data to support this assumption).
- The HSE data provided average weights for different age bands. This meant that, especially for the 16-24 age band, the lower age weight was likely overestimated, and the upper age weight was likely underestimated. For example, the company's approach resulted in a jump in weight from 43.9kg at 15 to 59.1kg at 16 year of age. The EAG preferred to linearly interpolate the 16-24 age band between the age 15 weight and the HSE 25-34 age band.

The administration costs of fosdenopterin also depended on administration setting. The company omitted neonatal critical care costs (which are expected to be relevant to MoCD Type A) in the base case because these costs are not expected to differ between arms. The company claimed that neonatal critical care costs were included as a scenario analysis for the

fosdenopterin arm. The EAG agreed that neonatal critical care costs would not be expected to differ between arms and that including neonatal critical care costs in the first cycle would have a negligible impact on the ICER.

Standard of care costs

The company calculated drug costs for the standard of care as medications to control seizures. The company selected the ten most frequently used anti-seizure medications (ASMs) from the pooled study data from their four trials to inform SOC costs, which were sourced from the electronic Market Information Tool (eMIT) 2022[36] where possible, or the British National Formulary (BNF)[37].The proportion of patients from each arm that were modelled as requiring these ASMs was calculated by the company as the proportion from each arm of the trial data that required at least one of the ten most frequent medications. The company claimed that the cost per day for these medications was then calculated as a weighted average of the cost of the ten medications selected, however the EAG noted that this cost was calculated as a simple average.

The EAG agreed that ASMs would be required for standard of care patients, as the clinical data suggested that seizures are common for MoCD Type A patients and clinical input to the EAG confirmed that ASM usage would be necessary for some people with MoCD Type A. The EAG believed that the ten most frequent medications from the trials were sufficient to capture possible medications used. The EAG noted that the estimated proportions requiring anti-seizure medications were extremely similar between the arms. However, EAG analysis suggested that this small difference made a negligible difference to results.

The EAG noted some errors in the company's calculation of cost per day for children, where the child dose per day for nitrazepam and diazepam were multiplied by the weight of patients when these doses should not have been weight based. In addition, the child dose per day of phenobarbital should have been weight based, but the company did not account for patient weight in its dose cost. These errors were corrected by the EAG.

The EAG also noted an error in how the company calculated drug acquisition costs in the model where the company applied half cycle correction to survival before calculating drug acquisition costs for both arms. In addition, drug costs were not calculated by the company in cycle 0. The EAG considered this approach to be inappropriate since in practice fosdenopterin and drugs for

SoC would be acquired at day 0 and at the beginning of each subsequent cycle. This approach was applied in the EAG base case.

The EAG's primary concern with the company's approach to SoC costs was the assumption that patients on SoC receive only one anti-seizure medication, an assumption which the EAG considered to be too low. In taking a simple average of the costs for the ten most frequently used ASMs the company assumed that patients received only one medication at average cost, yet this assumption was not justified.

However, the company's own calculation of proportion of patients requiring these medications calculated based on those patients on one or more ASMs, implying that some patients were on more than one ASM. In addition, the EAG noted a systematic literature review from Dravet syndrome found that the mean number of ASMs was 2.20 - 3.14 in these patients[38], and clinical input to the EAG confirmed that MoCD Type A patients who were experiencing seizures would be expected to be on multiple ASMs. Although Dravet syndrome may be characterised by a higher seizure rate than MoCD Type A, the EAG believed that for the proportion of patients with MoCD Type A receiving ASMs the comparison to Dravet syndrome would be relevant, as the company argued in other areas of the submission such as for HRQoL. Clinical input to the EAG confirmed Dravet syndrome as an acceptable proxy for MoCD Type A. The EAG acknowledged that given the seizure severity in Dravet syndrome, the preferred assumption was the lower bound of the SLR estimate at 2.2 ASMs for the proportion of patients receiving ASMs in the model.

4.2.8.2. Subsequent treatment costs

The company did not include subsequent treatment costs in the submission, as people were assumed in the model to receive fosdenopterin for the duration of their life, and the control arm received SOC treatment. The EAG agreed that subsequent treatment was not relevant to this appraisal.

4.2.8.3. Health state costs

Health state resource use and costs presented by the company comprised of nasogastric feeding, required tests and specialist visits. Costs were taken predominantly from the NHS reference costs 2021/22[39]. The company confirmed at clarification that the costs for nurse visits, dentist visits and institutionalisation were updated from the Personal Social Services Research Unit (PSSRU) 2021[40] to the PSSRU 2022[41]. The only resource use cost obtained outside of

these sources was the cost for a low protein diet which was taken from a 2015 paper and inflated to 2022[42]. This cost was only applied as a scenario analysis, justified by the company due to uncertain efficacy and limited clinical use of a low protein diet.

Proportion of patients requiring nasogastric feeding was informed by the proportions of patients from each arm that were not feeding orally at their last study visit. Fosdenopterin patients were assumed not to require nasogastric feeding after 1 year of age, which the company justified based on clinical opinion. The EAG noted and corrected an error in the company's model which meant this assumption was not implemented, and instead nasogastric feeding was assumed to be required in every year except year 1. The company varied the estimated proportions of patients for each arm requiring nasogastric feeding in sensitivity analyses, but no scenario was provided where the fosdenopterin arm still required nasogastric after 1 year. The EAG noted that this assumption had significant implications for the total costs for the fosdenopterin arm, as assuming continued nasogastric feeding requirement would represent an additional £392,108 in undiscounted costs.

No healthcare resource data was collected for fosdenopterin, so the proportion of patients requiring tests was taken from the MCD-502[1] study by the company and applied equally across both arms. These tests were assumed to be administered [redacted] in the first year and [redacted] per year in the following years. Unlike for nasogastric feeding, the company did not assume any difference across arms in proportions of patients requiring tests or number of tests required.

The EAG noted that using the MCD-502[1] study appeared to be the most appropriate source for informing proportion of patients requiring tests given the limited resource use data available. The EAG agreed that assuming equal proportions across arms was justified. The EAG noted that the assumption that test frequency was lower after 1 year was not justified by the company. However, EAG analysis found this assumption to have a negligible impact on incremental costs, as SoC patients had a higher proportion requiring tests but fosdenopterin patients were estimated to have greater survival.

Specialist appointment requirements were estimated by the company using NICE TA614[32] as a proxy, since no specialist appointments were recorded in the clinical trials[32]. These were split by patients less than or greater than 12 years of age and sourced for the patients with a seizure frequency under 8 per day. The company claimed that this seizure frequency was consistent with the seizure frequency observed in the MoCD Type A patient-level data. Appointment frequencies were assumed to be equal across arms. The company's assumptions around

specialist appointments were reviewed by the company's clinical expert, who recommended the addition of metabolic medicine appointments to prescribe and monitor the dose of fosdenopterin.

The EAG noted that the comparison of seizure rates between the MoCD Type A patient-level data and TA614 was limited due to the difference in seizure measurement (seizures per day vs seizure status), but that the group from TA614[32] with the lowest seizure rate was an appropriate source to estimate specialist appointments. The EAG agreed with the assumption that specialist appointment frequencies were equal across arms. However, the EAG did not agree with the company that metabolic medicine appointments should be required equally for the SoC arm in the model. The clinical opinion given to the company only justified the addition of metabolic medicine appointments for patients receiving fosdenopterin. The EAG preferred to assume zero visits to a metabolic physician for the SoC arm.

4.2.8.4. Adverse event costs

The company sourced costs for adverse events (AEs) from the NHS reference costs 2021/22[39]. The rates of adverse events per year were taken "from the patient-level data from the clinical trial programme" according to the company. The EAG assumed that the same approach to AE related utility decrements was used, where given the absence of AE data from the SoC arm the AE rates were assumed to be equivalent across arms other than AEs specifically related to fosdenopterin administration.

As stated in section 4.2.7.2, the EAG agreed that 'Injury, poisoning, procedural complications' and 'product issues' were rightly omitted from the SoC arm due to being directly related to the administration of fosdenopterin. However, the EAG also considered that the company could have also omitted 'General disorders and administration site condition' as an adverse event cost to the SoC arm, since this AE likely relates specifically to the administration of fosdenopterin. The EAG found that that this would significantly impact results.

4.2.8.5. Other costs

An additional cost of £7,828 for terminal care was applied by the company as a one-off cost for patients transitioning to the 'dead' state. The company sourced this value as the average cost per child of the range stated in Noyes et al. 2013[43] and inflated the value to 2023.

4.2.9. Uncertainty

The company provided three types of sensitivity analysis as part of their submission:

- Probabilistic sensitivity analysis (PSA) to explore parameter uncertainty inherent within the model
- Deterministic sensitivity analysis (DSA) considers changes to the model, independently from one another, to explore key drivers of model results
- Scenario analysis explores some of the structural uncertainty related to the settings used in the company base case

The assumptions used to vary each parameter in the PSA or DSA were reported in Section B 3.7.2 of the CS.

4.2.9.1. Probabilistic sensitivity analysis

In the company's PSA they simultaneously varied parameters associated with uncertainty based on a specified distribution and measure of uncertainty and recorded the results of 5,000 iterations. The results were then used to generate average results, a PSA scatterplot, and a cost-effectiveness acceptability curve (CEAC). Although the EAG notes that the average results were generated erroneously, with the average of each ICER being taken, rather than calculating an ICER from the average incremental costs and QALYs.

At clarification stage, the EAG asked the company to check and re-run its PSA to address some parameters having omitted uncertainty estimates included (clarification questions B23 and B24). The company addressed the uncertainty in the utility values and drug costs, though the latter was without using the reported standard deviations from the NHS eMIT. Nevertheless, the EAG does not consider it likely that any further amendments to the PSA inputs would markedly affect the interpretation of the results.

4.2.9.2. Deterministic sensitivity analysis

The company's DSA set each parameter to its upper and lower bound in turn. The company then presented the parameters that caused the greatest variation in the ICER in a tornado diagram. As part of the EAG's review of the DSA, several issues were identified:

- The DSA considers a combination of both structural and parameter uncertainty. For example, utility values were varied according to their lower and upper limits, aligned with

the published source used, whereas other items included in the DSA referring to enabling or disabling model features (e.g., enabling or disabling administration costs), or arbitrarily varying input parameters at ±10% of the input value. This makes interpretation of the findings somewhat challenging, as it is not immediately clear which items are more (or less) realistic than others.

  - Of note, in most instances the structural uncertainty had a far greater impact on model results than any one parameter.

- Some parameters are varied which are not technically associated with any uncertainty. For example, the cost of fosdenopterin is varied at ±10% of the input value, but this is a fixed price proposed by the company. While not reflective of 'true' uncertainty, this type of analysis can at least highlight key model drivers, though the specific findings should not be misinterpreted as being indicative of uncertainty in the model results *per se*.

- Input cells were inconsistently linked to the parameter sheet of the company's cost-effectiveness model. In instances where the inputs were not linked the varied value did not get included in the calculations meaning the uncertainty was not captured.

4.2.9.3. Scenario analysis

The company's scenario analysis explored the impact of employing alternative selections for a number of the model controls. The scenarios were automated using Visual Basic for Applications (VBA). These included some of the common scenarios such as alternative time horizons and discount rates, as well as more specific scenarios such as assuming 1% fosdenopterin discontinuation. The full list of scenarios can be seen in Section B.3.9.3.

Programming errors meant that the automated scenario analysis results did not align with those produced by running the scenarios manually. The company revised some of the programming at clarification stage, however some scenarios were still inaccurate. This was often related to some controls not passing through the parameter sheet as required for the VBA code to function as intended.

5. COMPANY'S COST-EFFECTIVENESS RESULTS

5.1. Company's base-case cost-effectiveness results

The results presented in this report incorporate a PAS discount for the technology of interest (fosdenopterin) and list prices for all other treatments (i.e., ASMs), no comparator interventions had a PAS. The PAS for fosdenopterin is a [redacted]% simple discount on the list price. The results reported by the company are shown in Table 20, generated using the company's updated model provided following the clarification stage of the appraisal. The deterministic and probabilistic results are provided, with incremental cost-effectiveness ratios (ICERs) of £[redacted] and £[redacted] per QALY gained respectively, for fosdenopterin versus SoC.

Table 20: Company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICER
Company deterministic base case					
SoC	£201,652	10.22	-	-	-
Fosdenopterin	[redacted]	29.01	[redacted]	18.79	[redacted]
Company probabilistic base case*					
SoC	£207,728	10.26	-	-	-
Fosdenopterin	[redacted]	29.05	[redacted]	18.80	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; SoC, standard of care.

Note: *The 'average' probabilistic ICER was originally calculated by the company by taking the mean of all ICERs. The EAG has corrected this in the table above by re-calculating the mean ICER based on the mean incremental costs and QALYs.

For highly specialised technology (HST) appraisals, the standard willingness-to-pay threshold (λ) is £100,000 per QALY gained, though a QALY weight between 1 and 3 can be applied based on the magnitude of modelled benefit.[44] Further details about this are provided in Section 9 of this report. However, whichever QALY weight is assigned, the company's base-case analysis generates an ICER in excess of what would normally be deemed a cost-effective use of NHS and PSS resources.

5.2. Company's sensitivity analyses

The company undertook probabilistic and deterministic sensitivity analyses, to demonstrate the uncertainty around the base-case results. These are discussed in turn in the sub-sections that

follow. Of note, [redacted].

5.2.1. Probabilistic sensitivity analyses

The mean results of the PSA are presented alongside the deterministic results in Section 5.1 and are comparable to the deterministic results. The PSA scatterplot and CEAC are re-produced in Figure 6 and Figure 7, respectively, reflecting edits made by the company to its model following the clarification stage of the appraisal. The PSA scatterplot shows a near linear relationship between the magnitude of QALYs gained and the incremental costs associated with fosdenopterin, which is expected given that the model reflects only one 'alive' health state in which all costs are incurred. The CEAC shows that [redacted] of PSA iterations are associated with an ICER that would be considered cost-effective at a λ of £100,000 to £300,000.

Figure 6: PSA scatterplot (re-produced by EAG)

Abbreviations: EAG, external assessment group; m, million(s); PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 7: CEAC (re-produced by EAG)

Abbreviations: m, million(s).

5.2.2. Deterministic sensitivity analyses

Separately to the probabilistic analysis, the company provided results from a deterministic sensitivity analysis (DSA). Like with the PSA, [redacted]. As expected, the key parameters that influence the model results relate to the specification of annual discount rates, the model time horizon, the cost of fosdenopterin, and long-term utility estimates.

5.2.3. Scenario analysis

The company provided scenarios exploring some of the structural uncertainty related to the model. As reference in Section 4.2.9.3, some scenarios generated by the models automated scenario analysis code did not align with the scenarios when implemented manually. The company scenarios that could be verified by the EAG are presented in Table 21.

Table 21: EAG reproduced scenarios

Scenario	ICER	% change in ICER
Base case	[redacted]	
Joint survival model using log-logistic parametric survival model	[redacted]	-4.32%

Scenario	ICER	% change in ICER
0% annual discount rate for costs and outcomes	[redacted]	29.41%
5% annual discount rate for costs and outcomes	[redacted]	-9.57%
5-year time horizon	[redacted]	-49.84%
10-year time horizon	[redacted]	-54.09%
1% fosdenopterin discontinuation per year	[redacted]	9.82%
Caregiver disutility per year of 0.05	[redacted]	31.95%
Differential nasogastric feeding as described in clarification response B18	[redacted]	17.27%

5.3. Model validation and face validity check

The company explained in its submission that internal quality assurance measures were undertaken throughout model development, using extreme value testing and formula auditing to ensure the consistency of model estimates (CS Section B.3.12.1, p.133). In addition, the company also sought input from a clinical expert and a health economics consultant on the model structure and inputs, following any identified errors were amended, though overall the company explained that no issues were identified with the structural or computational accuracy of the model (CS Section B.3.12.1, p.133).

The EAG identified several important errors in the company's model as part of its review, which calls into question the robustness of the company's model validation process (though the company did not provide any specific details concerning this process). Where applicable, the EAG has addressed errors it identified to inform the EAG's preferred base-case analysis (details of which are provided in Section 6.1 of this report).

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the EAG believes are more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Modelling the different outcomes of fosdenopterin patients
- Assumptions around the carer requirements of fosdenopterin patients
- The cost of wastage

In Section 0, the EAG base-case is presented based on a combination of the exploratory analyses presented in Section 0.

6.1. EAG corrections and adjustments to the company's base case model

The EAG addressed a number of errors that were identified in the company's base case model. These are described in Table 22.

Table 22: EAG corrections and adjustments to the company's base case model

Description	Company approach	EAG approach
Drug costs		
Correction of weight-based dosing	Child dose per day for nitrazepam and diazepam were multiplied by the weight of patients. The child dose per day of phenobarbital did not account for patient weight in its dose cost	Child dose per day for nitrazepam and diazepam were not multiplied by the weight of patients and the child dose per day of phenobarbital accounted for patient weight in its dose cost, in line with the products' labels
Half cycle correction applied to drug costs	Company applied half cycle correction to drug acquisition costs	Removed half cycle correction for this calculation

Description	Company approach	EAG approach
Caregiver utility		
Caregiver disutility does not consider survival	The disutility for caregivers is applied as a flat disutility over the time horizon and does not account for patient survival	Accounted for patient survival in calculations when applying carer disutility
Caregiver disutility is double count	Caregiver disutility applied in calculation of caregiver utility that feeds into caregiver QALYs. Caregiver disutility also applied in calculation of patient QALYs	Caregiver disutility is applied in the calculation of caregiver utility that feeds into caregiver QALYs. Caregiver disutility is then not applied in the calculation of patient QALYs
Number of caregivers applied in the fosdenopterin arm	Calculation of caregiver disutility for fosdenopterin calculated the caregiver bereavement disutility using the SoC number of carers (1.8) rather than the fosdenopterin assumed number (1)	Calculation of caregiver disutility for fosdenopterin applied the caregiver bereavement disutility using the fosdenopterin number of carers (1)
Incorrect discount rate applied to caregiver utility	The discount rate for the previous cycle was applied to the current cycle in the calculation of discounted caregiver QALYs	[redacted]
Caregiver survival double counted when deriving bereavement disutility	When estimating caregiver QALYs the company double counted the mortality of caregivers	Applied caregiver mortality once
General population mortality		
General-population mortality applied at the wrong rate	The yearly mortality rate was converted to a 6-month mortality rate and applied in each 1-month cycle	The yearly mortality rate converted to a 1-month mortality rate and applied every cycle
Correction to general population mortality cap	General population mortality applied additively to disease-related mortality	General population mortality applied as a cap to disease-related mortality
General population survival was derived without considering different mortality rates between sexes	General population mortality was calculated assuming a constant split of male and female patients	General population survival of males and females was derived separately, the distribution of males and females over time was then tracked to more accurately capture general population survival
Patient utility		

Description	Company approach	EAG approach
Correction to AE disutility	AE disutility calculated as a yearly decrement but applied per cycle (only included as a scenario)	AE disutility converted from a yearly to a monthly decrement before being applied each cycle
Model structure		
Correction of cycle length calculation	The cycle length was inconsistent calculated throughout the model	Cycle length aligned to one average month (365.25/12 days)
Other		
Correction to application of nasogastric feeding assumption	In the CS, nasogastric feeding was assumed to be not required in the fosdenopterin arm after 1 year, but in the model the company model applied nasogastric feeding costs only after year 1	Nasogastric feeding costs in the model aligned with the assumptions in the company CS to be applied only in year 1 for the fosdenopterin arm

Key: AE, Adverse event; ASM, Anti-seizure medication; CS, Company submission; HSE, Health survey for England; QALYs, Quality adjusted life years; SLR, Systematic literature review; SoC, Standard of care

After applying the corrections in the model, the deterministic and probabilistic ICERs with the company base case were [redacted] and [redacted] per QALY gained, respectively.

Table 23: EAG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost (£) per QALY gained
Company deterministic base case					
SoC	[redacted]	14.42	-	-	
Fosdenopterin	[redacted]	31.93	[redacted]	17.51	[redacted]
Company probabilistic base case					
SoC	[redacted]	14.49	-	-	
Fosdenopterin	[redacted]	31.92	[redacted]	17.44	[redacted]

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

6.2.1. Using time to non-oral feeding to proxy disease deterioration

The company assumes that all fosdenopterin patients that survive beyond one year experience many outcomes equivalent to the general population. These outcomes include general population utility, no exposure to nasogastric feeding and near general population survival if the

company's base case log-logistic model is used to extrapolate OS. The EAG was concerned that there is limited evidence to support these expectations. To the contrary, evidence of time to non-oral feeding (Figure 4) suggests that the health status of fosdenopterin patients may in fact deteriorate over time, despite treatment.

Considering this, the EAG explored using the time to non-oral feeding data as a proxy marker of fosdenopterin patients whose outcomes are more akin to SOC than the general population. Patients that are feeding orally have been modelled as having improved outcomes, in line with what the company applied to all patients. This is still subject to substantial uncertainty, but the EAG's clinical expert suggested it was a plausible scenario for patients who received rapid intervention at birth. Patients that begin feeding non-orally retain the survival outcomes associated with the fosdenopterin arm but are assumed to have the same quality of life as the patients in the SOC arm.

The company provided the time to non-oral feeding data in the form of a KM plot in response to clarification question B18. By digitizing this figure the EAG has estimated that the median time to non-oral feeding for patients on fosdenopterin is approximately 75 months (6.25 years). An exponential model has been fitted to this data to extrapolate time to non-oral feeding beyond the observed period.

All of the settings impacted by this modelling are described in Section 0.

6.2.2. Utility assumptions

When modelling the long-term utility of patients in the SOC arm, the company applied a multiplier derived from Ara & Brazier [28] to the utility values estimated for adolescent Dravet patients (0.43) reported in Lagae et al.[27] The EAG prefers to use the adult utility value (0.34) for patients aged 18 years and then apply the multiplier from this point. Table 24 presents the EAG preferred utility values for patients in the fosdenopterin and SOC arm up to the age of 20, at which point the values slowly decrease in line with general-population utility values. The table also reflects the preferred assumption for fosdenopterin patient utility. Like the company, the EAG also assumes utility values for MoCD Type A may be similar to those obtained from a population with Dravet syndrome for the first year of life, despite there being no empirical evidence to support this assumption.

After the first year of life, for people that receive fosdenopterin, the company assumed that the average utility value would return to that of the age- and sex-adjusted general population. Given

the frequent use of anti-seizure medication for people treated with fosdenopterin, the EAG feels this is likely to be an overestimate of the average utility value of people treated with fosdenopterin that survive until at least 1 year of age. The EAG instead assumed that people treated with fosdenopterin would have a utility that is 50% better than patients on SOC relative to the general population. While arbitrary, the EAG considers that this is perhaps more likely to reflect the average utility for people that are still alive after 1 year of treatment, given the EAG's previous commentary concerning non-oral feeding and irreversible brain damage.

The EAG also explored applying a disutility associated with the use of fosdenopterin over a lifetime for several reasons. Firstly, to receive fosdenopterin every day, a permanent catheter is required through which the intervention is intravenously administered. This may be uncomfortable for people with MoCD Type A and may be associated with infection risk. Furthermore, there may be a mental health impact of having a constant, visible reminder of an MoCD Type A diagnosis due to the need for a permanent catheter. In addition, day-to-day activities, such as travel, would likely be restricted by the need for people with MoCD Type A to be in close proximity to a medical grade freezer which fosdenopterin needs to be stored in. While these factors may be considered relatively unimportant versus the implications of not being treated with fosdenopterin, the EAG believes that they would likely impact the health-related quality of life of people with MoCD Type A, relative to the general population that do not have a diagnosis of MoCD Type A.

To reflect this, the EAG modelled a decrement of 0.004 per cycle (equivalent to 0.048 per year), that was sourced from a paper by Matza et al,[45] which principally explored the disutility associated with intravenous infusions for people with bone metastases. The EAG does not consider this setting in its base case given that it already models a reduced utility compared to the general population for people receiving fosdenopterin. However, the EAG believes that such a scenario may be relevant if the company's assumptions related to long-term utility (i.e., per the general population) were preferred.

Table 24: Trajectory of patient utility values

Age	SOC		Fosdenopterin	
	Value	Source	Value	Source
0	0.330	Lagae *et al.* (2018)[27]	0.330	Lagae *et al.*, (2018)[27]
1	0.330		0.648	A 50% improvement
2	0.460		0.712	

3	0.460		0.712	from the SOC arm relative to the general population
4	0.460		0.712	
5	0.460		0.712	
6	0.430		0.696	
7	0.430		0.696	
8	0.430		0.696	
9	0.430		0.695	
10	0.430		0.695	
11	0.430		0.694	
12	0.430		0.694	
13	0.430		0.693	
14	0.430		0.693	
15	0.430		0.692	
16	0.430		0.691	
17	0.430		0.691	
18	0.340	Lagae *et al.*, (2018)[27] 12-17 value with decline proportional to general population	0.645	
19	0.339		0.644	
20	0.339		0.643	
…	Continued decline		Continued decline	

Abbreviations: SOC, standard of care

6.2.3. Carer disutility

The company assumes that fosdenopterin patients place no care burden on parents beyond the age of 5 years old as any care would be managed within a specialised schooling environment. The EAG considers this is likely to be implausible and at a minimum children with MoCD Type A will require support with administering fosdenopterin until they are much older. The EAG's clinical expert speculated that people treated with fosdenopterin may require less support if they received the intervention soon after birth (and experience child development as per the general population without MoCD Type A).

The burden on carers for people with MoCD Type A receiving fosdenopterin is uncertain and therefore the EAG has again leveraged the time to non-oral feeding to consider the outcomes of two divergent groups. Patients that are able to feed normally are assumed to be much closer to the general population than MoCD Type A patients on SOC. The EAG has optimistically assumed that these patients would have reduced care requirements, with the EAG assuming a single carer providing part time (half of the base-case estimate of 14.8 hours) care up to the age

of 18. For patients that require non-oral feeding, the EAG does not expect that these patients can be differentiated from MoCD Type A patients on SOC. Therefore, non-oral feeding patients are assumed to require the same fulltime and lifetime care requirements from 1.8 carers.

6.2.4. Anti-seizure medication

The company has assumed that any patient receiving ASM only receive one type of medication. This assumption was not aligned with evidence from the trials used to support the company's submission, nor with the opinion of the EAG's clinical expert.

An SLR investigating Dravet syndrome reported that patients received between 2.20 and 3.14 ASMs.[38] The EAG recognizes that seizures are less of a defining characteristic of MoCD Type A than they are in Dravet syndrome, so has applied the cost of 2.20 anti-seizure medications for each patient using these interventions (i.e., the lower bound from the aforementioned SLR).

6.2.5. Appointments with metabolic physicians

The company modelled frequent visits to a metabolic physician for all MoCD Type A patients, with those up to the age of three visiting twice a year and then annually thereafter. The EAG's clinical expert suggested that patients on SOC would likely not visit a metabolic physician, and this would be unique to fosdenopterin patients. The EAG updated the model to reflect this (i.e., the cost was only applied to the fosdenopterin arm of the model in the EAG's analysis).

6.2.6. Application of weight data

The acquisition of fosdenopterin is the main cost in the model, and fosdenopterin's weight-based dosing makes patient weight a key driver. The company used three different sources to estimate how the weight of people with MoCD Type A changed with age:

- WHO data by month for patients less than four years old[33]
- Royal College of Paediatrics and Child Health UK-WHO growth charts for patients aged four years and over but below 16[34]
- HSE data for patients aged 16 years and older[35]

The source for adult weights, the HSE data, provides weights for wide age bands, with the first band being 16–24-year-olds. Because people are still growing in this band there is a wide variance between these age groups. This means that when compared to the weight data for 15-

year-olds from the Royal College of Paediatrics and Child Health there is a large jump in weight from 43.9kg at 15 to 59.1kg at 16 year of age. The EAG has linearly interpolated the HSE age 16-24 weight data, to smooth the change in weight across this band. This results in patient weight increasing from 43.9kg at 15 years old to 59.1kg at 24 years old in uniform increments.

The company has assumed that patients would be in the [redacted] percentile of weight due to the developmental impact MoCD Type A can cause. The EAG prefers to use data for the 25th percentile, as it reflects fosdenopterin having an effect on patients' development. This does mean modelling the SOC arm using the 25th percentile data too, but this has negligible impact on the results as the drugs that have weight-based dosing in the SOC arm are low cost.

6.2.7. Vial wastage

The EAG is concerned that in its current form fosdenopterin is associated with a substantial volume of unavoidable wastage. Fosdenopterin is supplied in 9.5mg vials and the recommended dose (in most instances) is 0.9mg/kg, with its label stating that once reconstituted fosdenopterin must be used within 4 hours.[14] Given that fosdenopterin is administered once per day, if treatment is given at home this means any remaining treatment will be wasted. In a hospital the wastage could only be avoided if there was more than one patient to allow for vial sharing, though this is unlikely given the prevalence of MoCD Type A.

The EAG has done an analysis using the company base case settings, fosdenopterin wastage costs sum to a total of [redacted] (discounted) over a lifetime horizon, of which [redacted] would be incurred in the first five years. The wastage in the first 5 years of a patient's life would equate to approximately 37% of the fosdenopterin they were provided. The EAG performed an exploratory analysis concerning the wastage costs if, hypothetically, a 3mg vial was also available. The resulting wastage costs totaled [redacted] over a lifetime horizon and [redacted] over the first five years – that is to say, a reduction in wastage of close to [redacted]% over a lifetime horizon.

Wastage could only be eliminated entirely by introducing impractically small vial sizes, which the EAG acknowledges would not be feasible. Nevertheless, wastage could be reduced if fosdenopterin were made available in a smaller vial size. The EAG highlights that this analysis should be considered as exploratory and illustrative only; and that for the avoidance of doubt, a 3mg vial (or indeed any other smaller vial size) is not available for fosdenopterin.

6.2.8. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.1 to 6.2.7 to the company's model. Each change was made individually. The EAG has made a significant structural development to the model by using time to non-oral feeding as a proxy for the health of fosdenopterin patients. Implementing this change has the following impacts on the model:

- The cost of nasogastric feeding is applied to those that are non-orally feeding across the whole time horizon
- Non-orally feeding patients have the same utility as those in the SOC arm and their carers have the same disutility as the carers of SOC patients
- Patients that feed orally are assumed to have a utility halfway between the SOC utility and the age- and sex- matched general population utility
- Patients who feed orally are assumed to require a single carer up to the age of 18, this carer is modelled as providing 50% of fulltime care

The results of the EAG's exploratory analyses applied individually are provided in Table 25.

Table 25. Exploratory analyses undertaken by the EAG

Scenario description	Section(s)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ company base case (£)
EAG corrected company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]
Early-onset MoCD Type A population	4.2.3	[redacted]	19.19	[redacted]	[redacted]
Exponential parametric survival model for fosdenopterin OS	4.2.4	[redacted]	14.36	[redacted]	[redacted]
Fosdenopterin patients have a utility halfway between SOC patients and general population	6.2.3	[redacted]	14.24	[redacted]	[redacted]
Using the utility value for adult Dravet syndrome patients for adult MoCD Type A patients	6.2.2	[redacted]	18.83	[redacted]	[redacted]

Scenario description	Section(s)	Δ Costs (£)	Δ QALYs	ICER (£/QALY)	Δ company base case (£)
Time to non-oral feeding to differentiate fosdenopterin patients	6.2.1, 6.2.3	[redacted]	9.90	[redacted]	[redacted]
Patients receive more than one anti-seizure medication	6.2.4	[redacted]	18.79	[redacted]	[redacted]
SOC patients do not visit metabolic physicians	6.2.5	[redacted]	18.79	[redacted]	[redacted]
Linearly interpolate weight data for patients aged 16-25 years old	6.2.6	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

The EAG's preferred assumptions

The EAG preferred base case ICER is £[redacted] per QALY gained. In the EAG's base-case analysis, an exponential model is preferred to estimate OS for people that are treated with fosdenopterin. Depending on the most plausible long-term survival extrapolation, taking into consideration the currently limited data to accurately project survival outcomes for all people with MoCD Type A treated with fosdenopterin, the specification of the log-logistic model may also be appropriate. Ultimately, as with many of the model settings and assumptions, the choice of survival curve is subject to substantial uncertainty.

Table 26. EAG base case

Preferred assumption	Section(s)	Cumulative ICER £/QALY
Company base case	5.1	[redacted]
EAG corrected company base-case	6.1	[redacted]
Early-onset MoCD Type A population	4.2.3	[redacted]
Patient weight is modelled using 25th percentile data	4.2.8.1	[redacted]
Linearly interpolate weight data for patients aged 16-25 years old	6.2.6	[redacted]
Patients receive more than one anti-seizure medication	6.2.4	[redacted]
SOC patients do not visit metabolic physicians	6.2.5	[redacted]

Preferred assumption	Section(s)	Cumulative ICER £/QALY
Using the utility value for adult Dravet syndrome patients for adult MoCD Type A patients	6.2.2	[redacted]
Fosdenopterin patients have a utility halfway between SOC patients and general population	6.2.2	[redacted]
Time to non-oral feeding to differentiate fosdenopterin patients	6.2.1 and 6.2.3	[redacted]
Exponential parametric survival model for fosdenopterin OS	4.2.4	[redacted]
EAG preferred deterministic ICER incorporating all of the above changes		[redacted]
EAG preferred probabilistic ICER incorporating all of the above changes		[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

Note: † This ICER is a possible alternative if it is believed that fosdenopterin will have an effect on patient survival that is pseudo-curative.

6.3. Conclusions of the cost-effectiveness section

The EAG has conducted a detailed review of the evidence submitted by the company to demonstrate the cost-effectiveness of fosdenopterin for people with MoCD Type A. Following resolution of some identified modelling errors several key model settings and assumptions were investigated as part of the EAG's review. A key issue with regards to the model developed to inform this appraisal remains however, concerning its inability to fully reflect the experience of a person with MoCD Type A. Despite this, the model was deemed as being potentially suitable for decision-making, albeit with substantial uncertainty owing to the rarity of MoCD Type A.

While the company's submission was deemed to be broadly aligned with the final scope issued by NICE, however the EAG considered that the model only captured the experience of people with early-onset MoCD Type A, as no data for people with late-onset MoCD Type A treated with fosdenopterin were included within the model.

Estimating long-term survival outcomes for people treated with fosdenopterin is extremely challenging, given the lack of long-term data to support modelling efforts. The company's model makes use of conventional methodology to produce extrapolations, though to produce reliable extrapolations, a large sample size with long follow-up would normally be needed. Without these features of the data underpinning the survival analysis, extrapolations may be reasonable, but also may not provide credible long-term estimates. The EAG advises caution when interpreting the long-term estimates of survival, and consideration of different scenarios may be beneficial

for decision-making, though the EAG was limited by the range of options provided within the company's cost-effectiveness model.

The cost of fosdenopterin represents the largest cost component included within the company's model, accounting for approximately [redacted]% of the total costs incurred in the fosdenopterin arm in the company's base-case analysis. The EAG highlighted that as fosdenopterin is expected to made available in only one vial size (9.5mg), is administered once daily, and that any remaining product must be disposed of each day, the model includes a large volume of product wastage. Through exploratory analysis, the EAG highlighted the potential for cost savings to be realised were fosdenopterin also made available in a smaller vial size.

The EAG was also sceptical of several of the key assumptions the company made in relation to the health-related quality of life of people receiving fosdenopterin, as well as their carers. The company's base-case settings were considered likely representative of an 'upper bound' of what may be plausible, as this represented a scenario wherein people with MoCD Type A would have their utility effectively returning to that of the general population. The EAG has not seen any evidence to definitively justify this in the company's submission. Conversely, the EAG considered that some data suggests that the lives of people receiving fosdenopterin are not the same as the general population without MoCD Type A. The EAG attempted to amend the company's model to capture a possible divergence in the outcomes of patients on fosdenopterin, though such analyses were subject to clear limitations related to the volume of the evidence base to inform the model.

The company's submitted base case analysis illustrated that, based on its submitted price (including PAS discount), the ICER for fosdenopterin versus SOC was in excess of what would normally be deemed a cost-effective use of NHS and PSS resources. After addressing errors in the cost-effectiveness model, the ICER increased further. Based on the EAG's preferred settings and assumptions, the ICER again increased further, with an EAG's preferred base-case ICER of £[redacted] per QALY gained.

7. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS

7.1. Summary of cost savings estimated within the CS

7.1.1. Costs to patients and carers

The company did not highlight any specific costs to carers associated with caring for a patient with MoCD Type A. However, the company did highlight the possible impact of being a full-time carer on an individual's financial stability.

7.1.2. Governmental costs

The company did not present, nor did the EAG identify, any relevant governmental costs associated with the provision of fosdenopterin.

7.1.3. Productivity losses

The company assumed that the care of an MoCD Type A patient requires fulltime care from, in most cases, two individuals. Although the number of carers required to support a patient with MoCD Type A is uncertain, the burden on any individual is likely to be very high. The EAG's clinical expert agreed with the company that an MoCD Type A patient would require fulltime care from at least one person. Due to this commitment the carer would be unable to work. It is also highly likely that any parents that become care givers would be of working age, given that MoCD Type A is often diagnosed shortly after birth.

7.2. Staffing and infrastructure requirements associated with the use of the technology

The EAG believes it is important to consider the logistics of supplying fosdenopterin in both the short- and long-term. The EAG's clinical expert stressed the importance of prompt intervention once a suspected case of MoCD Type A has been identified to maximise positive outcomes for patients. To ensure fast response, ideally fosdenopterin would be made available in all hospitals in anticipation of a potential diagnosis. However, even with fosdenopterin's two-year shelf life, the rarity of the disease would likely lead to a costly amount of wastage through unused product, or through use of fosdenopterin in suspected cases that are later found not to be MoCD Type A. The EAG highlights that the logistics of making fosdenopterin available in NHS practice likely warrants clear planning to ensure a balance is struck between prompt delivery and practicalities of making treatment available across England and Wales.

For patients to be able to receive fosdenopterin administration at home, a medical grade freezer is required for storage. The provision and maintenance of this equipment has not been considered in the economic model but would need to be outlined before home administrations of fosdenopterin could commence.

7.3. Budget impact

The EAG did not have any comments on the budget impact of fosdenopterin.

8. SUBMISSIONS FROM PRACTITIONER AND PATIENT GROUPS

One professional group submission was received by the EAG alongside the company submission.

8.1. Manchester Centre for Genomic Medicine

This professional group saw the main aim of treatment with fosdenopterin to be "to prevent or reduce brain injury with resulting disability and premature death" and considered that "the treatment abolishes the disease-causing effects associated with the metabolic disorder and can effectively halt disease progression". The key clinical benefits were seen as to: i) "prolong life", ii) "reduce the extent of brain necrosis with subsequent neurological impairment including blindness, severe spastic and dystonic tetraplegia and epilepsy", iii) "avoid lens dislocation and associated complications", and iv) "prevent xanthine urolithiasis". It was stated that there is a large unmet clinical need as there is no other disease modifying treatment available for MoCD and no defined treatment pathway or clinical guidelines. An international consensus guideline is expected to be published in the first half of 2024.

It was considered that the introduction of fosdenopterin would have a large impact on clinical practice. Key logistical challenges include: i) providing urgent access to diagnostic tests and to fosdenopterin administration, ii) documenting biochemical response to treatment using repeated blood and urine tests that are only available in specialist laboratories, iii) providing urgent access to brain imaging to establish likely prognosis and inform discussion about the indication for long-term continuation of fosdenopterin treatment, iv) training patients/carers in drug administration and maintenance of the partially implanted, surgically placed central venous line to administer the drug, v) ongoing assistance for patients/carers on long-term fosdenopterin treatment with storage of the frozen drug and ancillaries and possibly with daily intravenous administration, vi) regular medical reviews for patients on long-term treatment, vii) vigilance regarding line-related infection and septicaemia (which requires hospital visits with febrile illnesses), viii) multidisciplinary care support may still be required for significant neurological disability, which may still be encountered depending on the level of pre-existing brain injury.

The introduction of fosdenopterin into routine clinical practice would result in increased healthcare resource use to enable daily intravenous treatment. However, if treatment can prevent severe neurodisability, this will result in a subsequent decrease in healthcare resource use requirements for disability-related health problems and caring for a severely disabled child.

While fosdenopterin is expected to provide meaningful clinical benefit in terms of longer survival, avoidance of long-term ocular and renal complications, and timely treatment reducing the burden of disability, the professional submission considered that further investment is required to introduce the technology. Funding would be required: i) to expand access to rapid specialist biochemical and genetic testing, ii) for medical-standard frozen storage in the pharmacy and at home and for transport of frozen fosdenopterin to the patient's home, iii) adequate support from specialist pharmacy teams to administrate and dispense the product, iv) training and home care support (where needed). The EAG noted that none of these costs were captured in the company's economic model, and that the cost of expanding access to biochemical and genetic testing likely falls outside the remit of the economic analysis for this appraisal, despite being a potentially relevant cost for consideration by the appraisal committee.

9. QALY WEIGHT

Based on the NICE Manual, a QALY weight between 1 and 3 can be applied based on the magnitude of modelled benefit (i.e., number of QALYs gained) [44]. The company suggested that fosdenopterin qualifies for the maximum QALY weight of 3, based on 36.77 undiscounted QALYs estimated for the fosdenopterin arm of the model (excluding caregiver utility values), which translates to an effective λ of £300,000 per QALY gained.

The NICE Manual does not explicitly state whether the QALY weight should be determined based on a discounted or undiscounted QALY gain, nor does it explicitly refer to whether carer QALYs should be included or not. However, the EAG considered it appropriate to reflect the total undiscounted QALYs estimated including carers, as a full reflection of the expected benefits of fosdenopterin. As a minor clarification, the company cited a value of 36.77 which is the total QALYs for fosdenopterin, not the QALYs gained (which would be 33.35). Since both of these values are in excess of 30, a QALY weight of 3 may be appropriate (using the company's base-case analysis).

Throughout Section 6 of this report, the EAG explored key drivers of the company's estimated QALY gain, related to survival estimation and health-related quality of life inputs. In the EAG's preferred base-case analysis, the estimated undiscounted QALY gain is 9.61, which would mean a corresponding value for λ of £100,000/QALY gained. However, the EAG recognises that one of the most uncertain areas of the model relates to the extrapolation of OS. Using the log-logistic model, which may be an appropriate extrapolation but provides a highly optimistic projection of survival on fosdenopterin, results in an undiscounted QALY gain of 18.16. This corresponds to a λ of £180,000/QALY gained. Ultimately, the final decision for a QALY weight sits with the appraisal committee, and so the QALY weight specified may change depending on the committee's preferred base-case analysis (and corresponding estimated QALY gain).

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Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 29 April** using the below comments table.

All factual errors will be highlighted in a report and presented to the evaluation committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Intended use in presumptive rather than solely confirmed molybdenum cofactor deficiency (MoCD)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 15 the EAG states, "the company's cost-effectiveness model applies costs only for patients with a confirmed genetic diagnosis of MoCD Type A. This means that the model is likely to under-estimate the 'true' costs for fosdenopterin, if there are any patients that are treated for whom a later genetic diagnosis is revealed not to be MoCD Type A". Additionally, on page 96 the EAG states "Secondly, the model did not capture the potential added costs associated with use of temporary use of fosdenopterin for people with suspected MoCD Type A, for whom a later diagnosis may rule this out".	This statement needs to be amended to explain that [redacted]	[redacted] This is for the initial (emergent) treatment of newborns for whom a prenatal diagnosis was not available but clinical and biochemical or neuroimaging data suggested MoCD Type A was present. All treated patients and natural history patients in the analysis were genetically confirmed. The Company can	The EAG has revised the key issue to reflect the company's approach to providing fosdenopterin for suspected MoCD Type A cases.

		offer further clarification on patient disposition within the trials to assess the probability of presumptive treatment with fosdenopterin for conditions other than MoCD Type A. Moreover, the Company would like to reiterate the importance of early initiation of treatment with fosdenopterin to ensure optimal outcomes for patients, as demonstrated in the integrated summary of efficacy (ISE), furthermore this is a necessary condition of the use of fosdenopterin.	

Issue 2 Incorrect statement regarding the pathophysiology of the condition

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 22, the EAG state "The build-up of sulphite oxidase in particular leads to irreversible neuron degeneration and brain damage and, in most cases, early death."	This statement needs to be amended to "The lack of active sulphite oxidase which causes an increase in central nervous system (CNS) sulphites, SSC in particular that leads to irreversible neuron degeneration and CNS damage and, in most cases, early death."	This is a factually incorrect statement.	Amended as requested.

Issue 3 Inappropriate conclusion about genetic testing in the clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 25, the EAG raises concerns about the requirement of genetic testing for patients with a presumptive diagnosis in the SmPC (Summary of Product Characteristics), noting uncertainty about whether all participants in the ISE underwent genetic testing to confirm the diagnosis of MoCD Type A. This is incorrect. The company would like to clarify that all patients in the interventional studies MCD-501, MCD-201 and MCD-202 all received genetic testing for the condition and were withdrawn from the study if this confirmed that they do not have MoCD Type A. Patients who were withdrawn were not included in the full analysis set (FAS) of the ISE. Additionally, 37 untreated control patients had a genetic diagnosis of MoCD Type A; however the date of diagnosis	The statement "The SmPC says that any patients with a presumptive diagnosis have to have a genetic test to confirm the diagnosis. From the available evidence, it does not appear that this was required within the studies. There is uncertainty about whether all participants within the integrated efficacy analysis have the target condition, such that it would be confirmed by genetic testing" should be omitted.	This is an incorrect conclusion. All patients who remained in the MCD-501, MCD-201 and MCD-202 studies (n=15) all had genetically confirmed disease, and those in the natural history cohort (n=37) required genetic confirmation. This was a protocol requirement for the interventional studies and was a pre-specified criteria in the integrated analysis for the natural history study. There is no uncertainty regarding the presence of the target condition in patients within the integrated analysis, as all underwent genetic confirmation for MoCD Type A. Thus, suggesting otherwise is misleading.	This information was not provided in the CS. The EAG has amended for clarity in light of this new information.

was missing for seven patients in the FAS.			

Issue 4 Differences in systematic literature review methodologies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 29, the EAG states "Truncation and adjacency operators were not used, which would have expanded the search" which further alludes to the statement "It is likely that some relevant records may have been missed." This is a difference in methodology between the EAG and the Company. Truncation operators were not used, but this was covered by manually spelling out different forms of words ("dependence.af or dependency.af or dependent.af" instead of "dependen$.af"). It is misleading to state that records may have been missed due to this, as this is simply a methodological difference.	To address this discrepancy, it is suggested to revise the wording to indicate that the Company manually accounted for different word forms instead of using truncation operators. The Company also suggests that the "It is likely that some relevant records may have been missed" statement be omitted.	The proposed amendment aims to clarify the methodology used by the Company in the systematic literature review. Although truncation operators were not used, alternative measures were taken to ensure thoroughness in the search process. Providing this clarification addresses any concerns raised by the EAG regarding potential limitations in the search strategy.	The EAG has considered this comment and does not consider it to be a factual inaccuracy. The EAG holds to its position that the approach the company took may have resulted in some relevant records being missed.

Issue 5 Misleading conclusion about the data-cuts used in the clinical and cost-effectiveness sections

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 13 and page 42, the EAG state: “The survival analysis used to inform the economic model used the July 2019 data-cut, whereas the clinical effectiveness data used the October 2021 data-cut. The company said that the July 2019 data-cut is the latest one for which individual participant level data were available, however the EAG could not understand this rationale, as individual participant level data would be required to present the results in the clinical effectiveness section.” This is a misleading conclusion.	The company proposes the following clarification: "The survival analysis informing the economic model utilised the July 2019 data-cut, while the clinical effectiveness data relied on the October 2021 data-cut. The use of the July 2019 data-cut was due to the lack of availability of individual patient level data in the later cuts, which was necessary for use in the economic analysis. The analysis for the regulatory submission to the European Medicines Agency (EMA) did not require certain datasets. Since these datasets were not needed, the contract research organisation did not include them in the final package sent to Origin. Consequently, Sentynl did not have access to these datasets.	Origin/Sentynl prepared datasets for all studies and the Integrated Summary of Safety (ISS) and ISE with a 2019 data cutoff for submission to the Food and Drug Administration (FDA). However, datasets from 2020 and 2021 were incorporated into the Clinical Study Reports for MCD-201 and MCD-202, as well as the ISS and ISE for submission to the EMA. Origin did not have these updated datasets packaged because the EMA does not mandate this in their submission. Additionally, the statistics vendor did not provide these datasets to Origin/Sentynl. The amendment provides clarity regarding the selection of the July 2019 data-cut for the economic analysis. It highlights that the decision was contingent upon the availability of individual participant level data necessary for the economic model.	The EAG has considered this comment and does not believe there to be a factual inaccuracy. In the main report, the EAG has added the company’s clarification regarding its rationale for not having the updated data and the EAG’s comment on this. In the executive summary, the EAG has signposted to this information.

		Additionally, it addresses the discrepancy between data-cuts used for different analyses, offering transparency in the evaluation process.	

Issue 6 Typographical error surrounding time to sustained non-oral feeding

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 41, the EAG noted "that in response to clarification question B18, the company presented a Kaplan-Meier curve on time to non-oral feeding. The labelling of this figure was unclear, with the embedded heading on the figure saying it was time to sustained non-oral feeding and the separate heading on the clarification response saying it was time to oral feeding. The EAG understood that this figure, shown below as Figure 2, is about time to non-oral feeding."	The company propose to omit this statement.	This was a typographical error which had been resolved by the EAG.	The EAG has added text to clarify that the company has now confirmed that the EAG's understanding was correct.

Issue 7 Misleading conclusion about reliability of treatment estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 45, the EAG states "no test of proportional hazards was presented, meaning there is uncertainty whether the Cox models provided a reliable estimate of treatment effectiveness."	The statement should be omitted. A test of proportional hazards was conducted in the ISE, and this information can be provided upon request.	The proposed amendment seeks to rectify this misleading conclusion by clarifying that a test of proportional hazards was conducted. Omitting the statement relieves implications regarding the reliability of the treatment effectiveness estimates.	The EAG has considered this comment and considers there is no factual error. It is correct that no test of proportional hazards was provided in the CS and that this means the EAG was unable to evaluate whether the Cox models provide a reliable estimate of treatment effectiveness. This leads to uncertainty.

Issue 8 Incorrect conclusion on the number of anti-seizure medication used

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 92, the EAG states "The company has assumed that any patient receiving anti-seizure medications (ASMs) only receive one type of medication. This assumption was not aligned with evidence from the trials used to support	This statement needs to be amended to explain that the Company modelled a weighted average cost across ten different ASMs.	The EAG's conclusion is incorrect as it suggests that the company only included one medicine, whereas in reality, a weighted average of ten medications is incorporated. This amendment ensures accuracy and provides a more	The EAG has considered this comment and considers there is no factual error. The company refers to the statement made in section 6.2.4 explaining exploratory analysis of more than one

the company's submission, nor with the opinion of the EAG's clinical expert." This statement is incorrect.		comprehensive understanding of the approach taken by the company in the analysis.	ASM. The initial critique of the company's assumptions about ASM use is in Section 4.2.8 of the EAG report, the EAG maintains their position on this approach. By dividing the sum of the ten most frequent ASM costs by ten (i.e., calculating a simple average) the company implicitly assumed the use of only one ASM, which does not reflect the data.

Issue 9 Incorrect conclusion on the exclusion of caregiver quality of life (QoL) after age 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 18, the EAG reports that the Company assumption of no carer requirements after age 5 in the fosdenopterin arm is unlikely, as patients between 5 and 18 years old would be unable to carry out the complex process required to self-administer fosdenopterin.	The Company propose that the EAG include the Company's justification for excluding caregiver QoL after age 5 to account for children requiring specialised needs to be institutionalised, at which point the effects fall outside of the remit of the model.	The EAG's reporting of the Company's approach is incomplete and should not be considered in the absence of the Company's full rationale.	The EAG has added the company's justification, and critique of the justification, to all the relevant sections: Key Issue 8, 4.7.2.3 and 6.2.3.

Issue 10 Confirmation of nomenclature of the prospective FAS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 40, the EAG state "PFAS (referred to as Partial FAS not Prospective FAS in this part of the company submission and FAS."	The company would like to confirm that this should state prospective full analysis set.	Typographical error.	The EAG has added text to clarify that the company has confirmed this referred to the prospective FAS.

Issue 11 Consistency of naming of MoCD Type A

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 23, the EAG use "MoCA" instead of "MoCD Type A".	The Company propose that any instances of "MoCA" be changed to "MoCD Type A".	Preferred terminology for clarity and continuity throughout the document.	There was only one use of 'MoCA'. This was in the context of a systematic review that assessed MoCD (all types) not specifically Type A. This typographical error has been corrected.

Issue 12 Statement regarding matching approach is misleading

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 37, the EAG states "Genotype matching for the genotype-matched analysis set (GMAS) was conducted using a matching algorithm. Treated patients were firstly matched one-to-one with a patient from the untreated natural history cohort who had the same homozygous mutation." This statement is misleading, in that the matching was also one-to-many in that if there was more than one exact genotype match all were included.	The Company suggests that the text is changed to reflect the following: "Treated patients are matched with patients in the natural history study who have the same homozygous mutation. If a treated patient had more than one control in the natural history study with the same homozygous mutation, the treated patient was matched to each in a one-to-many fashion. Treated patients who did not have an exact natural history homozygous match were matched upon mutations with a similar anticipated impact on protein function. If a treated patient did not have an exact natural history homozygous match but did have more than one match with a mutation with a similar anticipated impact on protein function, the treated patient was matched to each in a one-to-many fashion."	For full factual accuracy, the Company suggests that this statement is amended.	Amended as requested.

Issue 13 Clinical expert opinion on survival extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 64, the EAG states that the Company did not provide any clear justification for using the exponential distribution in the base-case and that its selection contradicted the advice of a clinical expert, who considered that it was 'not plausible and reflective of long-term outcomes'	The Company would like the statement changed to state that according to the clinical expert, the range of extrapolations presented for the standard of care (SoC) arm is plausible for long-term outcomes (including the exponential).	Upon closer inspection, the Company noticed that the statement relating to the exponential not being a plausible extrapolation relates specifically to the fosdenopterin arm and was erroneously pasted to the clinical validation slide for the SoC arm. In light of this development, the Company would request that the EAG modify their statement.	The EAG has amended the text to make it clear that the clinical expert supported the use of any of the parametric survival models.

Issue 14 Double-counting in general population mortality

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 65, the EAG state that 'General population mortality was applied in the company's model in addition to disease-related mortality (i.e. there was a potential for	The Company request that another statement be added to reflect the fact that in their submission, they state that the potential for this double-counting is extremely small given that MoCD Type A does not constitute a large percentage of deaths in the general population.	The EAG's statement is incomplete and could be interpreted to mean that the Company's model and argumentation is not robust.	The EAG has considered this comment and there is no factual inaccuracy. The statement by the EAG is correct even if the risk is low, as suggested by the company.

double-counting of overall mortality risk)'			

Issue 15 Gender-weighted general population mortality

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 65, the EAG state that 'General population mortality was assumed to comprise of an even split of male and female patients, despite studies suggesting MoCD Type A is more prevalent in males, for whom life expectancy is generally shorter (compared with females), ceteris paribus'.	The Company request that the EAG change this statement to align with the Company's model, which calculated a weighted average for the annual general population mortality based on the proportion of females (~30%) in the trials.	The EAG's statement is misleading. Although this difference in prevalence was noted in 'Spiegel R, Schwahn BC, Squires L, Confer N. Molybdenum cofactor deficiency: A natural history. Journal of Inherited Metabolic Disease. 2022;45(3):456-69', it was stated that this imbalance was unexplained. This may have been due to small sample sizes associated with a small patient population. The Company would also like to note that in the interventional arm of the studies, there was a balance of male to female, and survival outcomes were similar in each group.	The EAG has amended the referenced point and Table 22 to reflect that the error corrected by the EAG was the use of a fixed split of male and female patients when modelling general population mortality, rather than an even split.

Issue 16 Use of the word 'sulphur' – typographical error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 60, the EAG state "Any damage caused to the brain by *sulphur* build-up".	Proposed amendment to "Any damage caused to the brain by *sulphite* build-up".	The use of 'sulphur' is a suspected typographical error.	Amended as requested.

Issue 17 Misleading statement on 'erroneous' calculation of average results in the probabilistic sensitivity analysis (PSA)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 80, the EAG states "In the company's PSA they simultaneously varied parameters associated with uncertainty based on a specified distribution and measure of uncertainty and recorded the results of 5,000 iterations. The results were then used to generate average results, a PSA scatterplot, and a cost-effectiveness acceptability curve (CEAC). Although the EAG notes that the average results were	The Company suggests that the final sentence "Although the EAG notes that the average results were generated erroneously, with the average of each ICER being taken, rather than calculating an ICER from the average incremental costs and QALYs" be modified to say that this approach is not erroneous but an alternative way to calculate the probabilistic ICER.	Average results were not generated erroneously. The Company used a slightly different approach to calculation of the average results. Using this approach does not affect the robustness of the model.	The EAG has made no amendment as there is no factual inaccuracy. Deriving the average of a ratio in the way implemented by the Company is incorrect[1,2].

generated erroneously, with the average of each incremental cost-effectiveness ratio (ICER) being taken, rather than calculating an ICER from the average incremental costs and quality-adjusted life year (QALYs)."			

Issue 18 Erroneous reporting of the PSA ICER

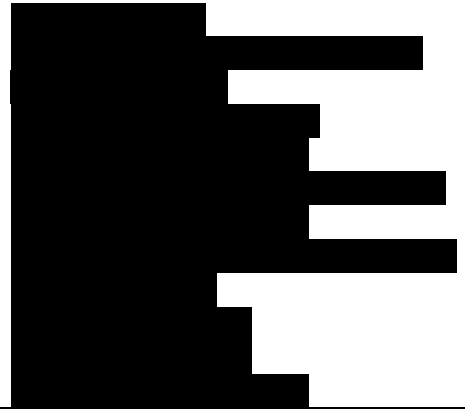
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 82, the EAG report the PSA ICER to be [redacted]	This ICER is not the one reported by the Company in their submission, and the Company suspect this estimate includes the modification of the approach to calculating the PSA ICER (see Issue 10).	The Company's submitted estimates were not accurately reported by the EAG.	The EAG has amended the results on this page to align with the probabilistic results from the Company's post clarification question model

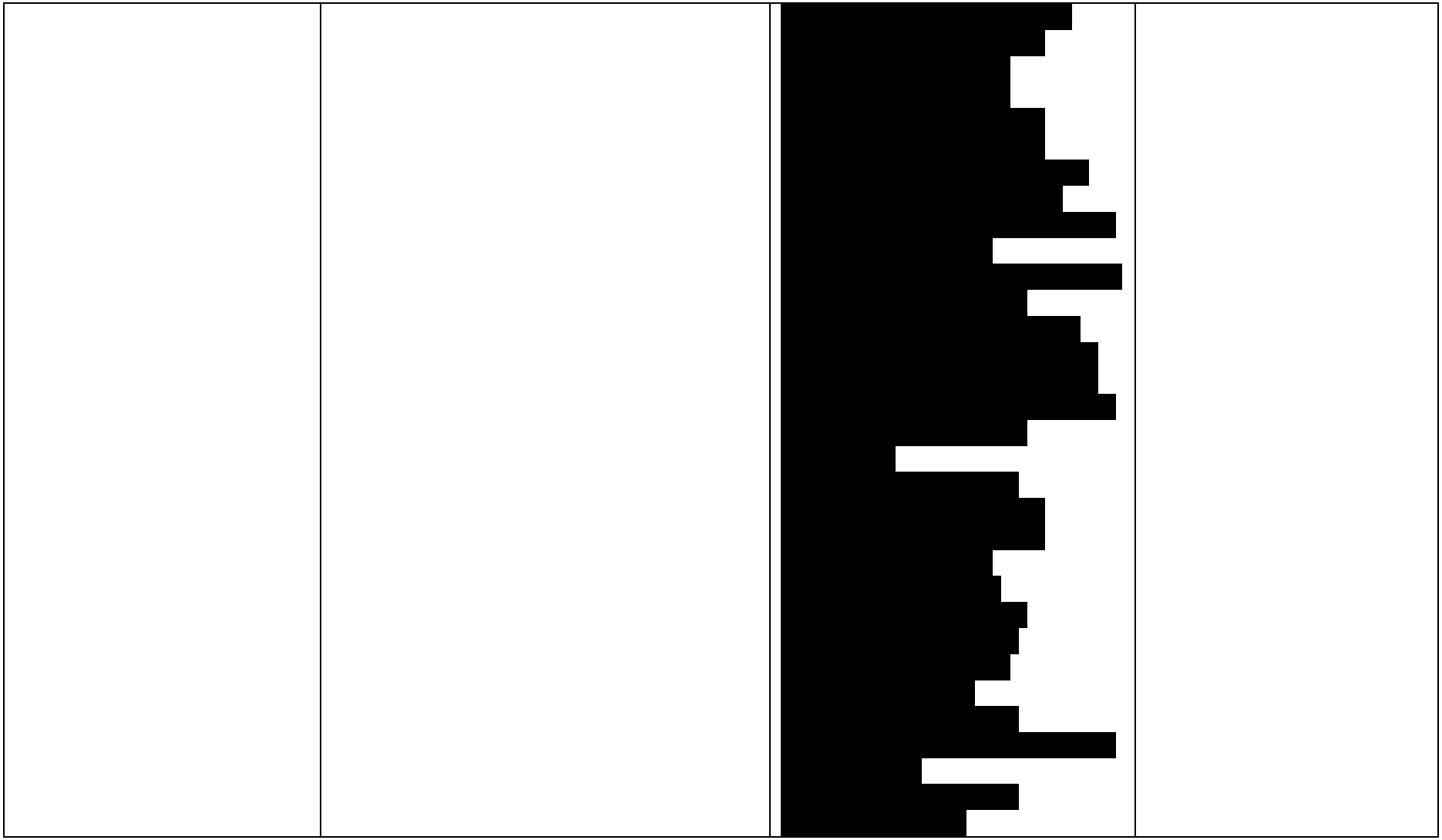
Issue 19 Statement regarding patients failing to achieve a normal weight

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 74 of the EAG report, the EAG quotes the company submission by saying "patients with MoCD Type A do not	The Company would prefer for the statement to be amended to "patients with MoCD Type A do not achieve normal	Upon reflection, the Company believes that the phrase "due to difficulty feeding" does not fully capture the comprehensive clinical context surrounding why	The EAG has considered this comment and considers there is no factual error and therefore will not amend the

achieve normal weight due to difficulty feeding".	weight", with the omission of "due to difficulty feeding".	patients with MoCD Type A fail to attain a normal weight.	quotation from the CS. The EAG has added text to acknowledge the company's reflection on this statement.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 78	Number of tests administered in the cost-effectiveness model.	[redacted]	This statement was originally made by the company on page 113 of the CS and was not marked CON. The EAG paraphrased the company's statement without CON marking in the EAG report. However, the company has now updated its report to redact this information. So, the EAG report has been amended. The EAG maintains that, as a modelling assumption, the assumed number of tests is not commercially confidential information.
EAG report, page 84	This may allude to the discount amount in the patient access scheme offered to NHS England.	[redacted]	This change has been actioned.

EAG report, page 12, 74, 75, 93	The company proposes that the mentions of 5th percentile weights in the base-case be marked as academic in confidence.	[redacted]	This information was not marked CON in the company's original submission. The EAG paraphrased the company's information without CON marking in the EAG report. However, the company has now updated its report to redact this information. So, the EAG report has been amended. The EAG maintains that, as a modelling assumption, patient weight is not commercially confidential information.
EAG report, page 60	The company propose for the modelling approach for feeding independently be marked as academic in confidence.		Information regarding feeding status, including time to non-oral feeding was not initially marked CON in the company's clarification response B18 Figure 5. However, the company has now updated its report to redact this information. So the EAG report has been amended.



		[redacted]	

1. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess. 1999;3(2):1-134.
2. Kohli-Lynch CN. Probabilistic sensitivity analysis and value of information analysis. In: Bishai D, Brenzel L, Padula W, editors. Handbook of Applied Health Economics in Vaccines: Oxford University Press; 2023.
3. National Institute for Health and Care Excellence. Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals. Process and methods; April 2023.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology evaluations (section 3.2) for more information.

The deadline for comments is **5pm** on **17 June 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	Grant Castor
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Sentynl Therapeutics, Inc.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the evaluation stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Not applicable.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainties related to non-randomised evidence and small sample size	No	The Company acknowledges the uncertainties associated with non-randomised evidence and the small sample size, however, the EAG stated that this is an issue intrinsic to the patient population. In the context of a rare and life-threatening disease like molybdenum cofactor deficiency (MoCD) Type A, ethical considerations justify the use of single-arm, open-label trials. These trials were designed in accordance with the European Medicines Agency (EMA) ICH Guidance E10, the United States Food and Drug Administration (FDA), and the current EMA guideline on Clinical Trials in Small Populations. The following measures were taken to minimise bias and ensure quality and comparability between the treated cohort with MoCD Type A (studies MCD-501, MCD-201 and MCD-202) and the sponsor-designed external control natural history study (MCD-502): 1. The decision to use an externally controlled (natural history) trial was aligned with EMA ICH Guidance E10, which permits such designs in cases where the disease course is predictable, and the treatment effect is dramatic. MoCD Type A, with its severe and life-threatening nature, meets these criteria, making an active comparator trial infeasible. 2. The studies focused on objective endpoints—overall survival (OS) and reduction of s-sulphocysteine (SSC) levels. These endpoints are clinically

		meaningful and directly associated with the disease pathology, providing robust measures of treatment efficacy. 3. To minimise bias and enhance comparability, the external control natural history study (MCD-502) included both retrospective and prospective components. This approach ensured a comprehensive representation of the MoCD Type A patient population and improved the reliability of the comparisons. 4. Data collection was standardised across overlapping geographic regions, and all prospective biomarker samples were analysed at a central bioanalytical lab. This consistency in methodology further strengthens the validity of the findings. 5. Treated patients were matched with external controls based on genotype, a stable baseline criterion unaffected by treatment, thereby reducing potential selection bias. 6. Extensive analyses were conducted to compare baseline characteristics and ensure similarity between treated and control cohorts. Multiple analyses on the OS endpoint, including Kaplan-Meier and Cox Proportional Hazards models, consistently demonstrated the treatment's survival benefit. Additional analyses addressed potential biases related to birth years and other variables.
Key Issue 2: Inconsistency of numbers included in the clinical inputs to the economic model	No	The Company acknowledges that there was some confusion regarding patient flow pertaining to different data cuts used, however the Company feel that these variation in patient numbers were adequately addressed in the clarification responses. Furthermore, the Company agrees with the EAG's observation that there were only minor differences between the datasets presented in the clinical evidence and the inputs used in the economic model. The Company hopes that the clarification responses provided helps the EAG better understand the aggregated analysis.

		Unfortunately, as stated in these responses, additional data from the October 2021 cut is not available and is not expected to become accessible to the Company.
Key Issue 3: Evidence for health-related quality of life from clinical evidence	No	The Company appreciates the EAG's concern relating to the adequacy of using a proxy condition to inform quality of life, and their concern that it introduces uncertainty in the model. The trials did not collect any quality of life data, and as already described in the submission, the Company did not identify any studies reporting quality of life in MoCD Type A as part of the systematic literature review and opted for searching a condition that closely relates to MoCD Type A (i.e. Dravet syndrome, another seizure-based condition). The EAG's proposed approach of conducting a health-related quality of life study is not feasible. Practical challenges arise due to the very small patient numbers, disease heterogeneity, and the rapid decline and short survival of untreated MoCD Type A patients. The decision to use Dravet syndrome as a proxy for quality of life in the initial Company submission was confirmed by a clinical expert during submission development. The Company subsequently sought clinical advice from [redacted] in formulating responses to Technical Engagement which suggested that Dravet syndrome is likely an upper bound of quality of life in untreated patients, given the relative differences in prognoses between Dravet syndrome and MoCD Type A. This is particularly linked to seizure frequency, as patients with MoCD Type A are likely to have daily seizures versus Dravet syndrome, where patients experience less frequent, acute attacks. As described in the Company submission, MoCD Type A is a severe and debilitating disease if treatment isn't initiated early, and quality of life is expected to be significantly impacted due to developmental delays and frequent, daily and disabling seizures. [redacted] suggested that another potential proxy for quality of life in MoCD Type A would be paroxysmal disorders, epileptic encephalopathies or Menkes disease, which have more relatable disease progression and severity patterns than Dravet syndrome. However, given small patient numbers in these disease areas, the literature on quality of life in these disorders is significantly more uncertain than the Company's base case using Dravet syndrome. The Company have therefore

		maintained their base case utilities, with the addition of the EAG's modification to use adult utilities from the age of 18.
Key Issue 4: Intended use in presumptive rather than solely confirmed molybdenum cofactor deficiency	No	The Company understands the EAG's concern that treatment in patients with disease suspicion adds uncertainty to the model outcomes. The Company does not expect there to be additional costs to the NHS (beyond those already incurred without the introduction of fosdenopterin). Any initial hospitalisations in the early days of life would occur regardless of diagnosis. However, the Company would like to note that NICE's Budget Impact Analysis included expert opinion for the number of patients that would undergo genetic testing for each positive diagnosis (n=[redacted]) and was therefore accounted for separately. Finally, as stated by the EAG, the initial treatment period until diagnosis does not represent a significant cost or driver of cost-effectiveness for patients who require a lifetime of treatment.
Key Issue 5: Use of fosdenopterin in the late-onset molybdenum cofactor deficiency type A population	Yes	The Company understands the EAG's concerns regarding the lack of evidence on the use of fosdenopterin in late-onset patients. New data has been published on the use of fosdenopterin in 2 children with late-onset MoCD Type A (Lund et al, 2024[1]) following the original submission. Treatment resulted in rapid biochemical and clinical improvement, with a favourable safety profile, much like those treated with early onset disease in the clinical trial. Given the small patient numbers and high unmet need in both early and late-onset patients, the Company urges the Committee to consider fosdenopterin in all patients with a clinical diagnosis of MoCD Type A. The EAG concluded that the economic model does not use sufficient data to inform the comparative effectiveness of fosdenopterin in all-comers. Consultation with a clinical expert ([redacted]) during Technical Engagement suggested that efficacy in late-onset patients is strongly warranted as there are measurable clinical improvements observed in treated patients. Late-onset patients are likely to have less brain damage and respond better to treatment (e.g. reduced seizures). As a result, the Company believe that current model results are generalisable to early and late-onset patients.

		Additionally, other HST submissions were granted reimbursement in a population broader than the evidence presented, based on the assumption that the mechanism of action would remain similar, such as odevixibat in progressive familial intrahepatic cholestasis (PFIC) (HST17). While PFIC is a milder disease, odevixibat was granted reimbursement in a broader population than was modelled and presented. In their submission, the Company provided evidence for two subgroups (PFIC 1 and 2). The evidence presented was considered sufficient to grant a positive recommendation in all subtypes of PFIC, despite the relative differences in disease presentation (e.g. efficacy of liver transplant, time of disease onset, which is generally later in PFIC 3 vs other subtypes, and speed of hepatic deterioration). Given the urgent need for treatment, small current patient numbers and under- and late diagnoses, there are practical limitations that mean carrying out a study in a sufficient number of late-onset patients for the purpose of this submission is not feasible.
Key Issue 6: Extrapolation of fosdenopterin overall survival data	No	As expressed by the EAG, the range of models presented for fosdenopterin are likely to present a plausible range for the long-term survival of patients treated with fosdenopterin but are subject to uncertainty given the small patient numbers and short duration of the trial. The Company also agrees with the EAG's conclusion that the survival extrapolations are unlikely to substantially alter the incremental cost-effectiveness ratio (ICER) (as demonstrated by both the Company's and EAG's scenarios).
Key Issue 7: Trajectory of quality of life for fosdenopterin patients	No	The Company acknowledges the EAG's conservative preference to opt for quality of life that is halfway between SoC and the general population in patients who are feeding orally. The Company sought advice from [redacted] to better understand the quality of life trajectory in MoCD Type A, which reaffirmed the Company's position that patients who are treated early experience fewer developmental delays, a higher likelihood to be feeding orally and therefore tasting food, and therefore can expect to have near-normal development and quality of life. The advice also suggested that, although there is a burden related to the daily administration of fosdenopterin, the impact on families and patients is comparable to other, more common conditions that require daily treatment. They also said that

		the families' experience is likely to be heterogeneous and therefore difficult to generalise and quantify, but that quality of life in patients treated with fosdenopterin for MoCD Type A would be near general population norms. It is therefore not appropriate to assume a 50% increment on the SoC trajectory for fosdenopterin-treated patients in the model base case. The Company have therefore maintained their base case and assume general population quality of life in fosdenopterin-treated patents.
Key Issue 8: The alleviation of caregiver burden	No	The Company acknowledges the EAG's concerns surrounding the assumption that caregiving is only required in treated patients until the age of 5. Expert opinion sought from [redacted] on the patient and caregiver experience in MoCD Type A suggests that, for most families, when treatment is initiated before the onset of severe brain damage, caregiving needs are similar to those of a healthy child once they are of school age, whereby the burden of administration falls within normal parental hours and care. Whilst fosdenopterin is administered daily through IV, the administration is not typically described as burdensome by families and could be considered comparable to other chronic conditions that require daily treatment. The assumption that caregiver disutilities stop at the age of 5 in the model is aligned with the experience of parents and caregivers of children who are treated with fosdenopterin. This implies that, although children are not administering fosdenopterin themselves, the administration falls within the same caregiving hours as caring for healthy children. Consultation with a clinical expert during Technical Engagement ([redacted]) also confirmed that the caregiving required in children with untreated MoCD Type A is extensive and distressing. In addition to this, [redacted] suggested that there is a significant burden to nurses, doctors and other medical support staff, as caring for children with MoCD Type A is distressing in the absence of treatment and is associated with significant moral distress and injury for medical staff. This is not captured within the model, but represents an additional burden to the NHS in the absence of treatment for MoCD Type A. At the request of the EAG, the Company also sought practical information on the implementation of any specialised care or schooling beyond the age of 5, in the

		event that a child with MoCD Type A would require formalised care once they reach school age. [redacted] provided examples of children who attended developmental clinics to support their development (from non-verbal to verbal, for example). These children are also likely to have additional support at school. Another example included attending a special needs school, however this patient started treatment later and has heightened developmental needs. To conclude, the Company believes the assumption of caregiver disutilities stopping at the age of 5 to reflect the experience of families is plausible and reasonable. Although the caregiver experience was described as variable from one family to the next, formalised caregiving exists outside of the remit of the family and children can benefit from additional support within the educational system where it is needed. This is therefore outside of the remit of the economic model and aligns with the Company base case.
Key Issue 9: Vial wastage	No	The Company appreciates the EAG's recommendation regarding vial sizes and possible strategies to reduce wastage, however there is currently no plan to introduce new vial sizes.
Key Issue 10: The ability of the cost-effectiveness model to reflect a patient's experience of molybdenum cofactor deficiency type A	Yes	The Company understands the EAG's concerns regarding the economic model, and its adequacy in reflecting patient outcomes in clinical practice. The model was initially validated by a clinician and has since been validated with [redacted] and [redacted] for the purpose of Technical Engagement. Although there are limitations and uncertainties in the model resulting from the rarity and severity of MoCD Type A, the model was well received and described as an accurate depiction of the patient and caregiver journey for MoCD Type A. In their model, the EAG modified the Company's model to assume that nasogastric feeding determines patient quality of life, and any patient who was feeding non-orally (regardless of their treatment arm) have the quality of life of the SoC arm. This results in a scenario which halved the incremental quality-adjusted life years (QALYs) predicted by the EAG's model compared with the Company base case (from ~19 to 9.9). The Company disagree with this approach, which disregards the

		other factors that constitute the quality of life of untreated patients such as seizures and developmental delays. As discussed with [redacted], nasogastric feeding is not a key determinant of outcomes and quality of life in MoCD Type A. Although a number of patients feed non-orally (including nasogastric feeding or gastrostomy tubes) in the fosdenopterin trial data, this is a result of irreversible brain damage, and reflects the speed of diagnosis and treatment initiation. Consultation with [redacted] confirmed that patients in the UK who initiated treatment with fosdenopterin early are feeding orally. Determining the impact non-oral feeding on quality of life is challenging in MoCD Type A as treated patients, despite feeding non-orally, have significant improvements on clinical milestones (such as gross motor function) vs untreated patients. Furthermore, treated patients who can feed orally have additional quality of life gains as they can taste and enjoy their food. Clinical opinion suggests that children with substantial central nervous system damage are more likely to feed non-orally (due to difficulty swallowing) and require respiratory support, which impacts their quality of life. The EAG's model includes a less conservative option assuming that patients who are not feeding orally have a 75% improvement in their quality of life in comparison with SoC (rather than the quality of life of SoC). The resulting scenario (applying the other changes found in Table 1) is an ICER of [redacted] (+[redacted]) on the Company's updated base case) versus [redacted] in the EAG's scenario. Instead of modelling patient quality of life based on oral feeding, a separate, more appropriate scenario reflecting seizure frequency has been included by the Company, where quality of life is linked to the average number of seizures per day from the trial data. A publication was sourced reporting EQ-5D utilities for 4 quartiles: seizure-free, 1 seizure per day, 2-5 seizures per day or 6 or more seizures per day (Wester et al, 2021[2]). On average, patients in the fosdenopterin arm had [redacted] seizures per day (rounded to [redacted]) and patients in the SoC arm [redacted]

		(rounded to [redacted]. Including the other changes to the base case, the resulting ICER is [redacted]. Despite these additional scenarios, the trial data is currently insufficient to accurately inform the link between nasogastric feeding or seizure frequency and quality of life or other long-term outcomes. The general scientific literature suggests that increased seizure frequency leads to brain damage, which in turn results in respiratory and feeding difficulties. Therefore, seizure frequency may offer a more informative model structure, but there is significant heterogeneity in both arms of the trial data preventing the Company from incorporating it adequately in the model. The introduction of either non-oral feeding or seizure frequency components increases the uncertainty of the results and should only be considered as informative scenarios, not as part of the model base case. The Company base case, which models survival as the primary outcome and derives quality of life from Dravet syndrome, has been validated by a clinician and a patient organisation. It is therefore the most reflective and least uncertain approach to predicting long-term costs and outcomes of fosdenopterin in MoCD Type A.

References: [1]Lund AM, Berland S, Tangeraas T, et al. Late-Onset Molybdenum Cofactor Deficiency Type A: A Treatable Cause of Developmental Delay. Pediatrics. 2024;153(6):e2023062548. [2]Wester V, de Groot S, Versteegh M, Kanters T, Wagner L, Ardesch J, Brouwer W, van Exel J; EPISODE-team. Good Days and Bad Days: Measuring Health-Related Quality of Life in People With Epilepsy. Value Health. 2021 Oct;24(10):1470-1475. doi: 10.1016/j.jval.2021.05.001. Epub 2021 Jul 3. PMID: 34593170.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 1 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base case incremental cost-effectiveness ratio (ICER)
EAG corrected company base case	[redacted]	The Company has applied the EAG's switch for model corrections	[redacted]
Key Issue 6: Exponential parametric survival	The fosdenopterin arm was extrapolated using the loglogistic distribution	Following the EAG's report, the Company applied the exponential distribution to the fosdenopterin arm	[redacted]
Using the utility value for adult Dravet syndrome patients for adult MoCD Type A patients	Adolescent utility values were used in adult patients	Following the EAG's report, the adult utility value (0.34) is used for patients aged 18 years and the multiplier is applied from this point	[redacted]
Linearly interpolate weight between 16 and 25 years old	The model did not linearly interpolate weight between 16 and 25	The model linearly interpolates weight between 16 and 25 as per the EAG's scenario	[redacted]

Company's base case following technical engagement (or revised base case)	Incremental QALYs: 12.38	Incremental costs: [redacted]	[redacted]

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

The updated probabilistic results are provided below for the Company's updated base case.

	Incremental costs	Incremental QALYs	ICER
Fosdenopterin vs SoC	[redacted]	12.15	[redacted]

Deterministic sensitivity analysis

The updated deterministic sensitivity analysis results are provided below for the Company's updated base case.

[redacted]

Scenario analysis

Additional scenarios around the Company's base case are provided below.

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base case incremental cost-effectiveness ratio (ICER)

Alternative scenario for Key Issue 10: Time to non-oral feeding to differentiate fosdenopterin patients	The model does not contain a link between nasogastric feeding and quality of life (QoL)	In contrast to the EAG's scenario, the Company believes a more appropriate scenario is to assume that QoL in patients not feeding orally is equivalent to 75% of the QoL in SoC, rather than equivalent to the QoL of SoC	Scenario: Fosdenopterin total costs: [redacted] SoC total costs: [redacted] Fosdenopterin total QALYs: [redacted] SoC total QALYs: [redacted] Incremental costs: [redacted] Incremental QALYs: 9.79 Incremental undiscounted QALYs: 19.93 ICER: [redacted]
Alternative scenario for patient QoL: linked to seizures	The model does not explicitly link QoL with seizures	The model uses seizure frequency to estimate QoL	Scenario: Fosdenopterin total costs: [redacted] SoC total costs: [redacted] Fosdenopterin total QALYs: [redacted] SoC total QALYs: [redacted] Incremental costs: [redacted] Incremental QALYs: 7.11 Incremental undiscounted QALYs: 13.69 ICER: [redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Updated cost-effectiveness analysis

July 2024

File name	Version	Contains confidential information	Date
Updated cost-effectiveness analysis	**V1**	**Yes**	**03/07/2024**

Contents

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B.1 Cost-effectiveness

B.1.1.1 Drug acquisition costs

Fosdenopterin

Costs associated with fosdenopterin are presented in Table 1. The acquisition cost of fosdenopterin is £1,206 per 9.5mg vial. A confidential patient access scheme (PAS) is included in the form of a [redacted] in the model.

Table 1. Fosdenopterin costs

Cost type	Unit cost
Fosdenopterin cost per vial (list)	£1,206
Fosdenopterin cost per vial (PAS)	[redacted]

Abbreviations: PAS = patient access scheme.

B.1.2 Summary of base-case analysis inputs and assumptions

B.1.3 Base-case results

B.1.3.1 Base-case incremental cost-effectiveness analysis results

Aggregated base-case results of the cost-effectiveness model are reported in Table 2. Disaggregated results are presented in Table 3 and Table 3. At list price, the base-case ICER is £1,971,011. With PAS [redacted]) the ICER is [redacted]. Given the undiscounted QALYs gained in the fosdenopterin arm (26.79 excluding caregiver utilities), fosdenopterin qualifies for a cost-effectiveness threshold of £267,900.

Table 2. Base-case results

	Fosdenopterin	SoC	Incremental
Total costs (list price)	£24,389,940	£186,147	£24,203,794
Total costs (PAS)	[redacted]	£186,147	[redacted]
Total undiscounted QALYs	26.79	3.72	23.07
Total QALYs	26.75	14.37	12.38
ICER (list price)			£1,955,485
ICER (PAS)			[redacted]

Abbreviations: ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years; SoC= standard of care.

Table 3. Disaggregated costs

	Fosdenopterin	SoC	Incremental
Undiscounted			

Drug acquisition	£62,630,871	£3,149	£62,627,722
Drug acquisition (PAS)	[redacted]		[redacted]
Disease management	£193,494	£233,014	-£39,520
Adverse events	£134	£38	£96
Terminal care	£59,193	£118,010	-£58,817
Total undiscounted	£62,883,692	£354,210	£62,529,481
Total undiscounted (PAS)	[redacted]		[redacted]
Discounted			
Drug acquisition	£24,277,933	£1,899	£24,276,034
Drug acquisition (PAS)	[redacted]		[redacted]
Disease management	£102,497	£155,300	-£52,803
Adverse events	£68	£29	£39
Terminal care	£9,442	£28,918	-£19,476
Total discounted	£24,389,940	£186,147	£24,203,794
Total discounted (PAS)	[redacted]		[redacted]

Abbreviations: ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years; SoC= standard of care.

Table 4: Disaggregated outcomes

Outcomes	Nulibry	SoC	Incremental
Undiscounted			
Life years	29.69	9.16	20.53
QALYs	26.79	3.72	23.07
Discounted			
Life years	15.06	6.96	8.11
QALYs	26.75	14.37	12.38

Abbreviations: ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life-years; SoC= standard of care.

B.1.3.2 Net health benefit

The net monetary benefit for fosdenopterin vs SoC is presented below.

Table 5: Net monetary benefit

	Value
Incremental QALYs	12.38
Incremental costs	£24,203,794
Incremental costs (PAS)	[redacted]
Net monetary benefit	-£20,490,578
Net monetary benefit (PAS)	[redacted]

Abbreviations: QALYs = quality-adjusted life-years.

B.1.4 Exploring uncertainty

B.1.4.1 Probabilistic sensitivity analysis

The probabilistic ICER is [redacted], which represents a 4.34% increase from the deterministic ICER and demonstrates that the uncertainty present in the model has

been controlled and accounted for. The ICER scatterplot of the 1,000 simulations is presented in **Error! Reference source not found.** and the cost-effectiveness acceptability curve is presented in **Error! Reference source not found.**.

Table 6. Results from the PSA

	Fosdenopterin	SoC	Incremental	% change from deterministic ICER
Total costs	[redacted]	£192,449	[redacted]	+2.42%
Total undiscounted QALYs	26.79	3.72	23.07	26.79
Total QALYs	26.75	14.37	12.38	-1.84%
ICER			[redacted]	+4.34%

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; SoC, standard of care.

[redacted]

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years.

Table 7. Proportion of simulations cost-effective

Threshold	% simulations cost-effective with PAS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: PAS, patient access scheme.

[redacted]

Abbreviations: PAS, patient access scheme; PSA, probabilistic sensitivity analysis

B.1.4.2 Deterministic sensitivity analysis

A deterministic sensitivity analysis was performed to examine the impact on the ICER for upper and lower bounds of included parameters. This was done through an automated one-way sensitivity analysis programme built for the model. A tornado diagram is presented in **Error! Reference source not found.**, and upper and lower bounds for the ten most influential parameters are reported in Table 8.

[redacted]

Table 8. Upper and lower bounds from one-way sensitivity analysis

Parameter	Range	ICER at lower bound	ICER at upper bound
Annual discount rate - costs (%)	[0.000 - 0.050]	[redacted]	[redacted]
Annual discount rate - benefits (%)	[0.000 - 0.050]	[redacted]	[redacted]
Model time horizon (years)	[10.000 - 100.000]	[redacted]	[redacted]
Discontinuation rate of Nulibry	[0.000 - 0.050]	[redacted]	[redacted]
Cost Nulibry	[redacted]	[redacted]	[redacted]
Patient characteristics - weight	[1.000 - 3.000]	[redacted]	[redacted]
Apply caregiver disutilities	[FALSE - TRUE]	[redacted]	[redacted]
Population	[Early onset patients - All patient set]	[redacted]	[redacted]
Include KM data	[FALSE - TRUE]	[redacted]	[redacted]
Utility Loss in Carers	[-0.126 - -0.154]	[redacted]	[redacted]
Patient characteristics	% female [0.275 - 0.337]	[redacted]	[redacted]
Nasogastric feeding Proportion - SOC - Y2	[0.603 - 0.737]	[redacted]	[redacted]
Terminal care cost (Death)	[8349.678 - 10205.162]	[redacted]	[redacted]
Apply AE disutilities	[FALSE - TRUE]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care; KM, Kaplan-Meier; AE, Adverse event.

B.1.4.3 Scenario analysis

Scenario analyses were conducted to analyse what impact different assumptions regarding model structure, treatment practice, utility values, could have on the results. Several scenarios were created to test the robustness of the ICER. The results of the scenario analysis are reported in Table 9. Applying QoL 50% of the general population in the fosdenopterin arm had the greatest impact on the ICER (+46%) followed by varying the time horizon (~-43%).

Table 9. Results from scenario analysis

Scenario	ICER	% change from base-case
Apply KM + parametric model	[redacted]	+2.48%
Joint models (loglogistic)	[redacted]	+20.26%
25th percentile weight	[redacted]	+12.76%
Discount rate=0%	[redacted]	+26.50%
Discount rate=5%	[redacted]	-7.83%
Time horizon = 5 years	[redacted]	-42.76%
Time horizon = 10 years	[redacted]	-43.88%
Caregiver disutilities excluded	[redacted]	+13.84%
Low protein diet included	[redacted]	-0.64%
Early onset population (N=33)	[redacted]	-3.79%
Discontinuation of fosdenopterin = 1% annual	[redacted]	+6.70%
Long-term fosdenopterin QoL = 50% equivalent of general population	[redacted]	+45.93%
Disutility of caregivers = -0.05	[redacted]	+5.54%
Differential nasogastric feeding in year 1 and year 2	[redacted]	+0.01%

Abbreviations: ICER, incremental cost-effectiveness ratio; KM; Kaplan-Meier; QoL, quality of life; SoC, standard of care.

B.1.5 Cost to the NHS and Personal Social Services

Costs

The annual cost of fosdenopterin is based on weight. Assuming a baseline weight calculated from the 5th percentile of patients, a weighted average cost per year is calculated using an acquisition cost per vial of £1,206 in the base-case and [redacted] at PAS price. The dose accounts for the number of vials per day in Year 1 and 2 compared with that in Years 3 to 5.

Table 10. Total cost of treatment without fosdenopterin

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
Fosdenopterin	£0	£0	£0	£0	£0
SoC	£902	£2,335	£3,436	£4,191	£4,653
Total	£902	£2,335	£3,436	£4,191	£4,653

Abbreviations: SoC=standard of care.

Table 11. Total cost of treatment with fosdenopterin

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
Fosdenopterin	£528,403	£1,447,712	£4,641,717	£6,245,473	£7,669,007
Fosdenopterin (PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	£0	£0	£0	£0	£0
Total	£528,403	£1,447,712	£4,641,717	£6,245,473	£7,669,007
Total (PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS=patient access scheme; SoC=standard of care.

Results of the budget impact model (BIM)

The total budget impact for fosdenopterin at is provided in Table 12 for the introduction of fosdenopterin across 5 years. Fosdenopterin is not expected to exceed the budget impact test of £20 million at 3 or 5 years.

Table 12. Total budget impact with PAS

	Year 1	Year 2	Year 3	Year 4	Year 5
Total/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total/patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Updated company PSA results

Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Undiscounted inc. QALYs	ICER (£/QALY)
SOC	[redacted]	14.43	-	-	-	-
Fosdenopterin	[redacted]	26.57	[redacted]	12.15	24.97	[redacted]

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology evaluations (section 3.2) for more information.

The deadline for comments is **5pm** on **17 June 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Metabolic Support UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the evaluation stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Metabolic Support UK received 15,700 GBP from Sciensus to contribute to Sciensus' work in understanding the MoCD type A diagnostic journey, review of their PASS study design and materials, identifying nurse-led intervention options and cross-border collaboration. This includes pass-through cost for community involvement.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainties related to non-randomised evidence and small sample size	**No**	This key issue is inherent to all ultra-rare disorders. While appropriate consideration should be given to the potential uncertainty caused by the non-randomised evidence and small sample size, it should also be acknowledged and understood that ultra-rare disorders will not see progression in treatment innovation or options when evidence requirements set for common disorders are also applied to ultra-rare disorders.
Key Issue 3: Evidence for health-related quality of life from clinical evidence	**No**	In line with key issue 1, while health-related quality of life (HRQoL) obtained from the MoCD type A population may have met evidence requirements set for common disorders, it would also have introduced uncertainty due to small sample size; which can be argued to be of a similar magnitude as the uncertainty introduced by using a proxy. We defer to healthcare professionals (HCPs) on the appropriateness of Dravet Syndrome as a proxy as this disorder is not within our area of expertise.
Key Issue 4:	**No**	

Intended use in presumptive rather than solely confirmed molybdenum cofactor deficiency		While we are not able to comment on the proportion of patients that are initiated and later revealed to be incorrectly diagnosed; we want to underscore that early diagnosis and initiation of fosdenopterin treatment is key to changing the outcomes of babies born with MoCD type A. Severe, irreversible brain damage often occurs within the first few days after a baby with MoCD type A is born. If fosdenopterin is not administered promptly upon suspicion of MoCD type A, babies will continue to experience severe, irreversible brain damage, limiting the effectiveness of fosdenopterin.
Key Issue 5: Use of fosdenopterin in the late-onset molybdenum cofactor deficiency type A population	**Yes**	We conducted a dedicated survey among community members affected by MoCD type A to collect information about key issue 5, 7, 8 and 9. Four community members provided insights into their experiences. Of them, three had experience with fosdenopterin, and two are currently care for a child with MoCD type A who is still receiving fosdenopterin. None of the responders had personal experience with late-onset MoCD type A. Separately, in communications with several HCPs who are treating people with MoCD type A, one physician shared a recent publication on the use of fosdenopterin in late-onset MoCD type A (Lund et al. 2024). In the article, two late-onset MoCD type A cases are detailed: The first, a girl who presented with developmental delays from 6 months of age, was diagnosed with MoCD type A at 15 months. Her gross motor skills continued to be delayed, though she was able to crawl, sit, stand and walk with support by 18 months. Her fine moto skills tracked normally. At age 33.4 months, the girl was enrolled in a clinical trial for fosdenopterin. Her motor skills and growth parameters have remained stable since treatment was initiated. Cognitive skills improved substantially, with 7 months of progression achieved in a period of 1.5 months, which was also recorded on the cognitive subtest of the Bayley Scales of Infant and Toddler Development, third edition (BSITD-3). At last follow-up, aged 5 years, no worsening had been experienced. However, a delay in receptive and expressive language was observed. The second, a boy, similarly presented with developmental delays, in terms of gross and fine motor skills, as well as language skills. He was diagnosed at 14 months and started receiving fosdenopterin shortly after. Within a month, he was able to feed himself, something he previously had not been able to do. At 30 months, gross and fine motor skills were normal, as were social and cognitive (BSITD-3) abilities. At last follow-up, aged 38 months, there were no signs of progression.

		We strongly urge that late-onset MoCD type A continues to be considered within the remit of this appraisal. Key issues noted around the non-randomised nature, small sample size and HRQoL evidence will be even more substantial if late-onset MoCD type A were to be considered as a separate indication. Moreover, as evidenced by Lund et al. (2024), treatment with fosdenopterin in children with late-onset MoCD type A is impactful and clinically relevant. Reference: Lund, Berland, Tangeraas, et al. 2024. Late-Onset Molybdenum Cofactor Deficiency Type A: A Treatable Cause of Developmental Delay. Pediatrics: 153(6):e2023062548.
Key Issue 7: Trajectory of quality of life for fosdenopterin patients	**Yes**	We conducted a dedicated survey among community members affected by MoCD type A to collect information about key issue 5, 7, 8 and 9. Four community members provided insights into their experiences. Of them, three had experience with fosdenopterin, and two are currently caring for a child with MoCD type A who is still receiving fosdenopterin. On the topic of quality of life, the families who are currently caring for a child with MoCD type A and receive fosdenopterin, shared: *"[His quality of life] is exactly the same as any other child. He goes to mainstream school. He is in school full-time. He feeds himself. We have no issues with fluids or drinking. The only thing we do have … he has got issues with his bowels. Other than that, he does everything. He goes swimming three times a week. The only limitation is that he needs to keep his line protected. I let him do everything. … He has always been developmentally delayed, but that does not stop him doing things. He has inclusive education that is tailored to him. He is doing exactly the same in ways that he can do it. … He is non-verbal. He has an AAC [augmentative and alternative communication] device and uses Makaton. He is starting to say words. He has been developmentally delayed from the beginning, so he is generally between 12 and 18 months behind. … He has never had seizures, never had any medication for seizures."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted] *"[She] is the oldest child [with early-onset MoCD type A] to start treatment at 9 weeks, causing most of the brain damage in those weeks prior. She has been stable and is living the worst part of the disease, but is*

		thriving with treatment, great care and love!" – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted]
Key Issue 8: The alleviation of caregiver burden	**Yes**	We conducted a dedicated survey among community members affected by MoCD type A to collect information about key issue 5, 7, 8 and 9. Four community members provided insights into their experiences. Of them, three had experience with fosdenopterin, and two are currently caring for a child with MoCD type A who is still receiving fosdenopterin. On the topic of caregiver burden, we asked families what the impact of MoCD type A is on them, especially after their child turns 5-years old: *"There is obviously aspects where life is impacted, for example giving his [fosdenopterin] medication every morning. … It has become our norm."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted] *"Every family and situation is unique and none exactly like the other. For me, I am a single mother that has had on and off nursing help but have been caring for her on my own. She is 24/7 care and does not go to school."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted] One of these families has other children, we asked for a comparison to life when the other children were five years old: *"It is exactly the same. Obviously, there are aspects; because of his [developmental] delay, I cannot allow him to go to afterschool club on his own, which I could do with them. … On a whole, if you look at him you would not know he is any different."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted]
Key Issue 9: Vial wastage	**Yes**	We conducted a dedicated survey among community members affected by MoCD type A to collect information about key issue 5, 7, 8 and 9. Four community members provided insights into their experiences.

		Of them, three had experience with fosdenopterin, and two are currently caring for a child with MoCD type A who is still receiving fosdenopterin. On the topic of vial wastage, we asked families about their experience with vial wastage: *"Any bits we don't use become clinical waste. As he has gotten older, the wastage has become less. Once we open up a new vial; once he gets a little bit bigger, we have to open up a third vial. It will be a bigger wastage that we have in that period, but it does change continuously."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted] *"[Her] current dose is [redacted]. When preparing [redacted], adding 5ml sterile water to each vial, you have a total of [redacted] of fosdenopterin. The total waste is 4.5ml. This calculation does change with current weight/dose on how much waste would be. As [she] gains weight, her dose would increase, causing less waste."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted] Separately, we also asked families whether they had any experience with previous formulations, considering that fosdenopterin has been investigated in different formulations over the past 12 years: *"He used to be on the original medication, the frozen version of the liquid. He moved over on the trial when he was about 18 months old. There was a lot more wastage. … For that, he also needed a pump to push it through his line, whereas now you manually push it through. This is [his] normal. He dislikes me touching his line, but he knows, in the morning, after he gets dressed, he has to have his medication."* – parent of a child with early-onset MoCD type A receiving fosdenopterin, [redacted]

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If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Willink Metabolic Unit, Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the evaluation stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Nothing to disclose**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Not applicable**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainties related to non-randomised evidence and small sample size	Yes	The small sample size and the selection criteria used in previous clinical trials create a significant risk of confounding. A controlled clinical trial including randomisation between a treated and untreated arm would not address the issue that clinical outcomes in typical MoCD-A vary greatly depending on the patient's state of health before fosdenopterin treatment is initiated, and much less on genotype, possible small variations in disease severity or other patient characteristics. The EAG have rightly pointed to the weaknesses of data presentation in the company's submission. These cannot be overcome with a different methodological approach to the available data. The treatment effects have been very consistent in the patients treated thus far when they are appropriately stratified according to their health state prior to treatment. It is unclear why the company chose to merge data of all treated patients in their analysis. Given the very small numbers of patients involved so far, a case-by-case analysis would likely be more helpful to draw conclusions about the cost-effectiveness of the intervention. The EAG could use evidence from publications and from lived experience both from parents of affected children and clinicians who used cPMP.

		[redacted] The case series published in 2015 [Schwahn et al. 2015] used previous siblings as untreated controls for children treated with cPMP and provides some evidence for the biochemical and clinical efficacy of the intervention.
Key Issue 2: Inconsistency of numbers included in the clinical inputs to the economic model	No	The presentation of data in the company's submission is inconsistent and confusing. Not all patients treated with fosdenopterin were included in the data analysis because of restricted access to the clinical trials. .
Key Issue 3: Evidence for health-related quality of life from clinical evidence	No	This could be resolved with a survey of existing patients via the patient support organisation Metabolic Support UK
Key Issue 4: Intended use in presumptive rather than solely confirmed molybdenum cofactor deficiency	Yes	To maximise clinical effectiveness, treatment of suspected cases has to be initiated prior to definitive diagnosis. This has also been proposed in recently published international guidelines [Schwahn BC, van Spronsen F, Misko A, Pavaine J, Holmes V, Spiegel R, Schwarz G, Wong F, Horman A, Pitt J, Sass JO, Lubout C. Consensus guidelines for the diagnosis and management of isolated sulfite oxidase deficiency and molybdenum cofactor deficiencies. J Inherit Metab Dis. 2024 Apr 16. doi: 10.1002/jimd.12730. PMID: 38627985.] The response to treatment can be assessed within a short period of time and inappropriate treatment can be swiftly discontinued. The company are currently providing fosdenopterin free of charge for a trial period of 4 weeks. The provision of cPMP/fosdenopterin has not been holding up treatment of new patients in the UK over the last 15 years.

		Storing fosdenopterin in major paediatric centres would allow rapid distribution to sites that want to treat new patients and a rotation of stock would allow the use of fosdenopterin for the treatment of existing patients prior to expiry, to reduce waste.
Key Issue 5: Use of fosdenopterin in the late-onset molybdenum cofactor deficiency type A population	No	The prevalence of atypical cases of MoCD-A, with late onset of clinical symptoms, is currently not known. Only a few patients have been identified and it may not be appropriate to treat all these patients with fosdenopterin, given the burden of treatment and the variability of their presentation.
Key Issue 6: Extrapolation of fosdenopterin overall survival data	No	Survival of patients will mainly depend on their health status prior to starting fosdenopterin treatment. Pre-symptomatically treated patients are at low risk of premature death whereas patients with severe brain injury prior to starting treatment will have a reduced life-expectancy, according to the severity of their disability. Not all patients will continue fosdenopterin treatment for life. Re-orientation of care may be an appropriate choice for some patients, especially in those with severe brain injury prior to starting treatment.
Key Issue 7: Trajectory of quality of life for fosdenopterin patients	Yes	The long-term clinical outcome and quality of life very much depends on the health state of the patient prior to starting fosdenopterin treatment. For almost all patient, their health status will not change much after the neonatal period. This issue should be addressed in the first instance by asking patients and their carers about their lived experience. The quality of life for pre-symptomatically treated patients is likely not substantially different from the general population, including for those who have additional needs. Not all patients on treatment require anticonvulsant medication.

Key Issue 8: The alleviation of caregiver burden	No	The administration of fosdenopterin and care for a totally implanted venous access device requires help from another person. This is however only required for a very short duration during the day. Some patients with typical MoCD-A and pre-symptomatic treatment can achieve independent living whereas others who were treated after onset of brain injury will require full time care and permanent supervision to assist with intermittent issues relating to dystonia, seizures or breathing difficulties. There is a clear dichotomy of long-term outcomes of treated patients.
Key Issue 9: Vial wastage	No	The vial price likely doesn't reflect production cost of the active ingredient and a price reduction for infants could be negotiated if no smaller vials are made available. However, most children will require a full vial after the end of the first year of life. There is no published evidence to justify the recommended optimum dose and previous treatment experience suggests that a range of dosing can be applied, which could help to reduce waste in older children. This is already reflected in current practice.
Key Issue 10: The ability of the cost-effectiveness model to reflect a patient's experience of molybdenum cofactor deficiency type A	No	More granular data on the outcome of treated patients is required to address this issue. It is disappointing that the company submission does not take into account how different the patient experience on treatment has been and has not attempted to stratify the patient cohort.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The company submission and subsequent EAG analysis does not adequately reflect the clinical effectiveness of the intervention.	6.3 Page 96	No	The analysis of clinical effectiveness does not differentiate between patients that are treated pre-symptomatically and those treated after onset of significant brain injury. Merging clinical outcome data of pre-symptomatically treated patients with those treated after experiencing major brain injury will not yield meaningful data for the assessment of clinical effectiveness, whether the sample size is small or large. This has been a major flaw in the company's evaluation of trial data used in their submission. Using this approach, the clinical effectiveness of the intervention will be systematically underestimated in the cohort of pre-symptomatically treated children and may be overestimated in those treated after the initial brain insult occurred.
Additional issue 2: The submitted data are not complete and do not reflect the accumulated clinical experience	All	No	Only a proportion of all treated patients has been included in the company's submission and data analysis. There has been no consideration of many other patients who were started on cPMP and whose treatment was discontinued.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR Sections 1.4 – 1.5. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 10 July.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Treating molybdenum cofactor deficiency (MoCD) type A and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Bernd Schwahn
2. Name of organisation	Manchester Centre for Genomic Medicine
3. Job title or position	Consultant Paediatrician
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with molybdenum cofactor deficiency type A? ☒ A specialist in the clinical evidence base for molybdenum cofactor deficiency type A or fosdenopterin? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose

8. What is the main aim of treatment for molybdenum cofactor deficiency type A? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Fosdenopterin is a causal treatment for MoCD-A and restores the activity of molybdenum cofactor – dependent enzymes to an extent that accumulating toxic substances, namely sulfite, S-sulfocysteine (SSC) and xanthine, normalise within hours of starting the treatment. The main aim of treatment is to 1) prevent or reduce disability due to sulfite-related acute toxic effects on the brain and 2) to reduce the risk of disease-related long-term complications and of premature death. The natural history of MoCD creates three different scenarios when treatment with fosdenopterin may be considered: A) the pre- or oligo-symptomatic fetus or newborn with severe MoCD-A (leading to a typical disease course after invariable progression to scenario B) B) the symptomatic fetus or newborn baby with severe MoCD-A in the first phase of the typical disease, with acute severe encephalopathy due to sulfite-related irreversible brain injury. C) the infant or older child with atypical, attenuated MoCD-A Patients with MoCD-A will fall in either of the three groups. In severe, typical MoCD, the time after birth before signs of sulfite encephalopathy are observed can vary between a few hours and a few days. Progression to severe irreversible brain injury then happens very quickly, often within hours. Some children with severe MoCD do not experience a distinct postnatal encephalopathic crisis but display milder signs of encephalopathy after birth. In those cases, postnatal brain imaging has revealed brain changes that suggest they have experienced a prenatal onset of severe encephalopathy. This has led to confusion over attempts to classify patients as “early-onset” or “late-onset” and correlate these groups with respective long-term outcomes.

	Depending on the starting scenario, the aims of treatment with fosdenopterin can be differentiated as follows: A) Fosdenopterin treatment can avert disease progression towards severe sulfite-related toxic encephalopathy and thus prevent most of the disability associated with untreated typical MoCD. Sequelae from sulfite encephalopathy such as epilepsy, dystonic cerebral palsy and developmental arrest as well as disease-related long-term complications such as ocular lens dislocation, xanthine urolithiasis and osteoporosis due to immobility and sulfite effects on bone tissue can be avoided. B) Epilepsy, cerebral palsy and developmental arrest will invariably be present, as a consequence of the previous acute sulfite-related brain injury. Treatment with fosdenopterin will prevent disease-related long-term complications such as ocular lens dislocation, xanthine urolithiasis and will help to reduce the extent of osteoporosis due to sulfite effects on bone tissue. C) Children in this group have variable but generally milder degrees of movement disorder and dystonia and sometimes also seizures. Fosdenopterin treatment corrects the biochemical abnormalities and may help prevent future acute neurological deterioration which has occurred in some children (akin to Leigh syndrome in disorders of mitochondrial energy metabolism). The extent of ameliorating effects on other neurological symptoms is currently unknown. Fosdenopterin treatment will prevent disease-related long-term complications such as ocular lens dislocation, xanthine urolithiasis and will help to reduce the extent of osteoporosis due to sulfite effects on bone tissue.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	1. Full biochemical response with normalisation of biomarkers 2. Evidence of developmental progress 3. Absence of intrusive seizures with or without anticonvulsant medication

	4. Absence of intrusive dystonic episodes with or without antispasmodic medication 4. Avoidance of lens dislocation and associated complications 5. Avoidance of xanthine urolithiasis and associated complications
10. In your view, is there an unmet need for patients and healthcare professionals in molybdenum cofactor deficiency type A?	There is a large unmet need. There is no other causal or even disease-modifying treatment for MoCD type A. Awareness of this rate metabolic disorder is not very high and diagnostic facilities to allow rapid differential diagnosis are not readily available.
11. How is molybdenum cofactor deficiency type A currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would fosdenopterin have on the current pathway of care?	**There are no UK guidelines available**. However, an international guideline was recently published, with participation of UK specialists [Schwahn BC, van Spronsen F, Misko A, Pavaine J, Holmes V, Spiegel R, Schwarz G, Wong F, Horman A, Pitt J, Sass JO, Lubout C. Consensus guidelines for the diagnosis and management of isolated sulfite oxidase deficiency and molybdenum cofactor deficiencies. J Inherit Metab Dis. 2024 Apr 16. doi: 10.1002/jimd.12730. PMID: 38627985.] **There is currently no defined pathway of care for patients with MoCD-A.** Symptomatic care is provided according to clinical need by multidisciplinary teams and the level of care varies depending on availability of services for complex paediatric neurodisability or palliative care. Medical care is commonly directed by paediatric metabolic specialists, paediatric neurologists, or community paediatricians. Some patients are subjected to special medical diets which have limited efficacy and require nutritional monitoring. Most patients suffer from severe dystonia and cerebral palsy and require recurrent supportive acute hospital admissions to treat intercurrent respiratory illnesses, seizures or dystonic crises.

	Symptomatic management of molybdenum cofactor deficiency type A usually comprises: • anticonvulsants for epilepsy • medication to reduce spasticity and dystonia • tube feeding to overcome inability to swallow • oxygen supplementation or non-invasive ventilatory support to help with upper airway obstruction • Physiotherapy and care support to prevent complications emerging from immobility • Palliative care support at end of life, typically required before the age of 5 years **The availability of fosdenopterin will have a large impact on current practice** - It will be imperative to provide urgent access to diagnostic tests and to the medication fosdenopterin to allow timely intervention and maximise the treatment benefit. - Once a clinical decision to start fosdenopterin treatment has been made, the biochemical response to treatment needs to be documented with repeated blood and urine tests that are only available in specialist laboratories. - Brain MR imaging is required urgently to establish the likely prognosis and to inform the discussion about the indication for long-term continuation of fosdenopterin treatment. - Once a decision has been reached to maintain the patient on long-term daily intravenous treatment with fosdenopterin, patients will require a partially implanted, surgically placed central venous line to administer the drug and parents/carers will have to be trained in drug administration and line care. Transition to home care may be assisted by community nursing teams.

	- Families of patients on long-term treatment will require ongoing assistance with transport and storage of the frozen drug and ancillaries and possibly with daily IV administration. - Patients on long-term treatment will require regular medical reviews. - Patients with a partially implanted central line will require vigilance regarding line-related infection and septicaemia. This requires visits to hospital with febrile illnesses. - Depending on the pre-existing brain injury, patients on continued treatment may still experience significant neurological disability and require multidisciplinary care support.
12. Will fosdenopterin be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between fosdenopterin and current care? • In what clinical setting should fosdenopterin be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce fosdenopterin? (for example, for facilities, equipment, or training)	Current care for MoCD does not include regular IV drug administration, regular blood or urine monitoring or frequent hospital assessments by specialist teams. Some children are exclusively managed in a supportive community environment overseen by community paediatrics and palliative care. They may require intermittent hospital admissions to treat intercurrent infectious diseases. Others may require non-invasive respiratory support, scoliosis surgery or other interventions as well as tertiary neurology support to manage epilepsy and dystonia. - Children who are receiving fosdenopterin treatment ***prior to*** experiencing brain injury do not require any of the above resources, however treatment needs to be monitored and the daily drug administration needs to be supported (see under Q 11) - Children who are receiving fosdenopterin treatment ***after*** having experienced brain injury will require many of the above resources, and treatment needs to be monitored and the daily drug administration needs to be supported (see under Q 11)

	Fosdenopterin can be administered in any paediatric inpatient or daycare setting, or after respective training, by home care nurses or carers at home. The treatment should be overseen by specialists in genetic metabolic disease. The following investment is likely required to implement wider access to fosdenopterin treatment: - Raising awareness and limited extra funding to expand access to rapid specialist biochemical and genetic testing. - Funding for frozen storage of fosdenopterin in pharmacy and at home, as well as for transport of the frozen product to the patient's home - Funding for adequate support from specialist pharmacy teams to administrate and dispense the product - Funding and training for home care support will be required in some cases.
13. Do you expect fosdenopterin to provide clinically meaningful benefits compared with current care? • Do you expect fosdenopterin to increase length of life more than current care? • Do you expect fosdenopterin to increase health-related quality of life more than current care?	Yes, treated patients will survive longer and will be able to avoid long-term ocular and renal complications. See also reply to Q8. - Patients treated prior to having experienced brain injury will be able to lead an almost normal life, without the burden of disability that is usually associated with the disease. - Patients treated after having experienced brain injury will be able to avoid long-term ocular, renal and potentially skeletal complications and will benefit from increased medical surveillance. They may also benefit from a reduced burden of seizures and dystonic crises.

14. Are there any groups of people for whom fosdenopterin would be more or less effective (or appropriate) than the general population?	Fosdenopterin will provide a biochemical normalisation in all patients affected with MoCD-A, but the clinical benefit of the technology will be much greater in patients treated prior to having experienced sulfite – related brain injury.
15. Will fosdenopterin be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This new treatment will completely change the current approach to patients with MoCD-A. The current supportive and often palliative approach will shift to an urgent, highly interventional approach. The diagnostic tests, skills and resources required to implement fosdenopterin treatment are already available in specialist paediatric metabolic services. Access to diagnostic testing will need to be facilitated for non-specialised neonatal units to shorten the time to diagnosis. Parents/carers will require a medical grade freezer at home and respective pathways for dispensing frozen drug to the home will have to be established.
16. Will any rules (informal or formal) be used to start or stop treatment with fosdenopterin? Do these include any additional testing?	Once a biochemical response has been established, the decision whether to continue the treatment with fosdenopterin in the long-term will largely depend on ethical and health-economic considerations. - Any patient with MoCD type A treated prior to having experienced irreversible brain injury will greatly benefit from continuation. - Patients who have experienced irreversible brain injury prior to starting treatment have so far all suffered from severe neurological impairment, whether treatment was continued or not, and their health benefits from continuation are limited. Given the invasiveness and likely cost of the technology, the benefit of long-term treatment needs to be weighed against the risk of daily IV drug administration,

	the burden of daily treatment for carers, and general resource implications of the technology for the NHS. The extent of irreversible brain injury should be assessed clinically and by performing a brain MRI scan during the first few weeks of life. Results can inform a clinical decision whether continuation of treatment is in the best interest of a family or not.
17. Do you consider that the use of fosdenopterin will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of fosdenopterin or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The health-related benefits for children treated with fosdenopterin prior to having experienced irreversible brain injury will be adequately reflected in QALY calculations (if they are assessed as a separate group). The situation for children treated after having experienced irreversible brain injury and suffering from severe neurological disability is more difficult to assess. Quantitative improvements in disease burden relating to seizures and dystonia or pain will be hard to measure. The benefit of preventing ocular or renal complications, which can create severe health problems if they occur, has not been captured in the proposed analysis. The incidence of acute glaucoma due to lens dislocation in untreated MoCD-A is not known. The incidence of xanthine nephrolithiasis should be comparable or higher than in isolated Xanthinuria where it is estimated that 40% of affected individuals experience this complication during their lifetime.
18. Do you consider fosdenopterin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is fosdenopterin a 'step-change' in the management of the condition? • Does the use of fosdenopterin address any particular unmet need of the patient population?	Fosdenopterin is highly innovative as the first causal treatment for MoCD-A [Schwahn B. Fosdenopterin: a First-in-class Synthetic Cyclic Pyranopterin Monophosphate for the Treatment of Molybdenum Cofactor Deficiency Type A (2021) touchREVIEWS in Neurology. 2021;17(2):85–91 DOI: https://doi.org/10.17925/USN.2021.17.2.85] It has the potential to transform the lives of affected children if treatment is started sufficiently early in the disease process.

19. How do any side effects or adverse effects of fosdenopterin affect the management of the condition and the patient's quality of life?	There are no known relevant drug-related adverse effects. Complications associated with daily IV administration and with the use of partially implanted central venous lines are to be expected and will impact on the quality of life. Such complications have however been manageable and become increasingly rare in the long-term treated patient population, especially after infancy.
20. Do the clinical trials on fosdenopterin reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The first cohort of UK patients treated with cPMP was described in a publication in 2015 [Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015;386(10007):1955-1963. doi:10.1016/S0140-6736(15)00124-5]. These patients were included in the retrospective data collection MCD-501 and surviving patients were included in the trial MCD-201. The trial MCD-202 recruited only a very small number of patients worldwide and none from the UK. Access to the clinical trials was limited to very few patients in the UK and selection of patients depended on local expertise and serendipity. UK patients are therefore over-represented in the existing clinical trials data. The patient selection included in the clinical trials reporting long-term outcomes is however not representative of the UK population of patients. It is biassed in favour of pre-symptomatically treated patients. Facilitated and unlimited access to fosdenopterin will increase the patient base and will likely result in more variable outcomes. The outcome of long-term treatment compared to trial data will depend on whether start and stop criteria will be applied. I am not aware of any adverse effects of fosdenopterin treatment other than those reported in the submission.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The immense benefit of treatment in some patients with early or pre-symptomatic treatment has not been adequately captured in the trial data. There are two recent case reports that highlight the benefits of fosdenopterin treatment Lund AM, Berland S, Tangeraas T, Christensen M, Confer N, Squires L, Brannsether B. Late-Onset Molybdenum Cofactor Deficiency Type A: A Treatable Cause of Developmental Delay. Pediatrics. 2024 Jun 1;153(6):e2023062548. doi: 10.1542/peds.2023-062548. PMID: 38808412. Schwahn BC, Hart C, Smith LA, Hart A, Fairbanks L, Arenas-Hernandez M, Turner C, Horman A, Rust S, Santamaria-Araujo JA, Mayr SJ, Schwarz G, Sharrard M. cPMP rescue of a neonate with severe molybdenum cofactor deficiency after early diagnosis owing to hypoglycemia and metabolic acidosis. t*o be submitted*]
22. How do data on real-world experience compare with the trial data?	Real world-experience critically depends on treatment criteria. The strong influence of the disease stage prior to treatment start on neurological outcomes is not reflected in trial data. The incidence of renal and ocular complications has not been adequately compared to control cohorts.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	Almost all known UK patients come from ethnic minority groups. Any decision over access treatment will therefore impact disproportionately on a minority of the population.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: **Uncertainties related to non-randomised evidence and small sample size**	The small sample size and the selection criteria used in previous clinical trials create a significant risk of confounding. However, a controlled clinical trial including randomisation between a treated and untreated arm would not address the issue that clinical outcomes in typical MoCD-A vary greatly depending on the patient's state of health before fosdenopterin treatment is initiated, and much less on variables such as genotype or possible small variations in disease severity due to other patient characteristics or environmental factors. The EAG have rightly pointed to the weaknesses of data presentation in the company's submission. These cannot be overcome with a different methodological approach to analysing the presented data, but rather with a different stratification of the data.
Key Issue 2: **Inconsistency of numbers included in**	No comment

the clinical inputs to the economic model	
Key Issue 3: **Evidence for health-related quality of life from clinical evidence**	A correlation between health state prior to starting fosdenopterin treatment and quality of life in terms of activities of daily living and QOL scales could be established by interrogating the company database or by a survey of families in the UK, facilitated by Metabolic Support UK.
Key Issue 4: **Intended use in presumptive rather than solely confirmed molybdenum cofactor deficiency**	To maximise clinical effectiveness, treatment of suspected cases has to be initiated prior to definitive diagnosis. This has also been proposed in recently published international guidelines [Schwahn BC, van Spronsen F, Misko A, Pavaine J, Holmes V, Spiegel R, Schwarz G, Wong F, Horman A, Pitt J, Sass JO, Lubout C. Consensus guidelines for the diagnosis and management of isolated sulfite oxidase deficiency and molybdenum cofactor deficiencies. J Inherit Metab Dis. 2024 Apr 16. doi: 10.1002/jimd.12730. PMID: 38627985.] The response to treatment can be assessed within a short period of time and inappropriate treatment in children who don't suffer from MoCD-A can be swiftly discontinued. The company are currently providing fosdenopterin free of charge for a trial period of 4 weeks. The provision of cPMP/fosdenopterin has not been holding up treatment of new patients in the UK over the last 15 years, despite uncertainty over funding. Storing fosdenopterin in major paediatric centres would allow rapid distribution to sites that want to treat new patients and a rotation of stock would allow the use of fosdenopterin for the treatment of existing patients prior to expiry, to reduce waste.
Key Issue 5: **Use of fosdenopterin in the late-onset molybdenum**	The prevalence of atypical cases of MoCD-A, with late onset of clinical symptoms, is currently not known. Only a few patients have been identified and it may not be appropriate to treat all these patients with fosdenopterin, given the burden of treatment and the variability of their presentation. A recent case report reports experience with this scenario.

cofactor deficiency type A population	Lund AM, Berland S, Tangeraas T, Christensen M, Confer N, Squires L, Brannsether B. Late-Onset Molybdenum Cofactor Deficiency Type A: A Treatable Cause of Developmental Delay. Pediatrics. 2024 Jun 1;153(6):e2023062548. doi: 10.1542/peds.2023-062548. PMID: 38808412.
Key Issue 6: **Extrapolation of fosdenopterin overall survival data**	Survival of patients will mainly depend on their health status prior to starting fosdenopterin treatment. Pre-symptomatically treated patients are at low risk of premature death. Patients with severe brain injury prior to starting treatment will have a reduced life-expectancy due to expected complications and health issues relating to severe cognitive and visual impairment, dystonia and immobility. Not all patients will continue fosdenopterin treatment for life. Re-orientation of care may be an appropriate choice for some patients with an increasing burden of co-morbidity.
Key Issue 7: **Trajectory of quality of life for fosdenopterin patients**	The long-term clinical outcome and quality of life very much depends on the health state of the patient prior to starting fosdenopterin treatment. For almost all patients on treatment, their health status will not change much after early infancy. This issue should be addressed in the first instance by asking patients and their carers about their lived experience. The quality of life for pre-symptomatically treated patients is likely not substantially different from the general population, including for those who have additional needs. Not all patients on treatment require anticonvulsant medication.
Key Issue 8: **The alleviation of caregiver burden**	The administration of fosdenopterin and care for a totally implanted venous access device requires help from another person. This is however only required for a very short duration of time during the day. Some patients with typical MoCD-A and pre-symptomatic treatment can achieve independent living whereas others who were treated after onset of brain injury will require full time care and permanent supervision to assist with intermittent issues relating to dystonia, seizures or breathing difficulties. There is a clear dichotomy of long-term outcomes and care needs of treated patients.

Key Issue 9: **Vial wastage**	The vial price likely doesn't reflect production cost of the active ingredient and a price reduction for infants could perhaps be negotiated if no smaller vials are made available. However, most children will require a full vial after the first year of life. There is no published evidence to justify the recommended optimum dose and previous treatment experience suggests that a range of dosing can be applied, which could help to reduce waste in older children. This is already reflected in current practice.
Key Issue 10: **The ability of the cost-effectiveness model to reflect a patient's experience of molybdenum cofactor deficiency type A**	More granular data on the outcome of treated patients is required to address this issue. It is disappointing that the company submission does not take into account how different the patient experience on treatment can be. More effort should go into stratifying the patient cohort.
Are there any important issues that have been missed in EAR?	PK/PD data regarding dosing and dosing intervals have not been considered. Patient stratification depending on health state prior to starting treatment has not been undertaken.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Fosdenopterin is biochemically effective in MoCD type A and it is safe to use

There is no other disease-modifying treatment available for patients with MoCD-A

Fosdenopterin can prevent brain injury and disability if treatment starts early in the disease

Patients with MoCD-A who have experienced brain injury can still benefit from treatment, although to a lesser extent

The data submitted by the company are confusing because they don't differentiate between patient subgroups

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Fosdenopterin for treating molybdenum cofactor deficiency type A [ID6264]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with molybdenum cofactor deficiency type A or caring for a patient with molybdenum cofactor deficiency type A. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 10 July.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with molybdenum cofactor deficiency type A

Table 1 About you, molybdenum cofactor deficiency type A (MoCD Type A) , current treatments and equality

1. Your name	Lucy Durrant
2. Are you (please tick all that apply)	☐ A patient with molybdenum cofactor deficiency type A? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with molybdenum cofactor deficiency type A? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Metabolic Support UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with molybdenum cofactor deficiency type A ? **If you are a carer (for someone with molybdenum cofactor deficiency type A) please share your experience of caring for them**	A case study of my son has been submitted for publication which details the diagnostic and care pathway. A copy has been attached in confidence. My son was born at 39 weeks after a problem-free pregnancy. He was born with no issues, other than that he refused to feed and had an increased startle reflex. The neonatal ward was concerned about this and did further testing, which was send off to Sheffield hospital (bloods and urine). At this point he was also found to have low sugar level based on a finger prick and received a glucose drip. At two days old, we were transferred to Sheffield hospital, where we received the MoCD type A diagnosis and the news that we were not eligible for fosdenopterin (cPMP) treatment because the trial had just ended. Within a few hours, our metabolic consultant, Dr Sharrard in Sheffield had managed to speak to Dr Schwahn in Manchester, who managed to sort something out and suddenly it was a completely different conversation. During this time an NG tube was also placed, and bolus feeds were started using a low-protein milk. The main focus at this point were ensuring his fluid and sugar levels were right. At three days old, we arrived at the paediatric intensive care where my son was monitored, he received an MRI etc. Because we arrived in the evening, treatment wasn't started until the next day, when he was four days old. At this point my son had not had any seizures but was very irritable and wouldn't feed. Within 12 hours his blood and urine tests were in normal range and he was much happier. He wasn't screaming all the time anymore and we were able to start breastfeeding. He was breastfed until 3 months old and then switched to bottle-feeding. Because he had been diagnosed with a cow's milk protein allergy, affecting his skin, he was

	prescribed a specialist formula. To this date he has a dairy allergy, but is otherwise not restricted in food. At approximately 3 weeks old, we were transferred back to Sheffield, where we continued to receive medication for a couple of nights. Once we were discharged, we had to travel to Sheffield every day to receive the medication, which is a 1.5hr roundtrip. It took a few more weeks before we were able to administer the medication at home, because we needed to get a medical grade freezer, pump and other supplies. We ended up buying the medical grade freezer ourselves because the NHS took so long to try and arrange it. Once we had all the equipment, we took a course to ensure we are trained to administer our son's medication and from that moment on hospital visits decreased. Initially we went twice weekly, then weekly, and by 6 months old we were on monthly visits. From that moment on, the main difference between my son and my other children is that he receives daily medication. Other than that, much of his life is similar to the rest of them. He went to a normal playgroup, normal nursery, mainstream school. We always try to keep life as normal as possible with him. Nowadays, we go to the hospital twice a year, once to Sheffield and once to Manchester. He is non-verbal and has been diagnosed as having a mild learning disability. It is unclear whether this is related to his MoCD type A or not. He also uses an augmentative and alternative communication (AAC) and a mobility pushchair and wheelchair; the latter mainly for his safety as he does not really have mobility issues. My son goes swimming three times a week and also goes to beavers. We bought a caravan (with a medical grade freezer) to enable us to go on holiday within the UK and now go about three times a month, since we can't go on holiday abroad. He does everything there as well, kid's club, playing on the beach, etc. It scares me to think about the future. I don't know whether he will be able to go to normal secondary school or paid employment.

	Looking at the MoCD community, there is another MoCD family whose child has started at a special secondary school and is doing really well there. Their child also did not start speaking until he was 8 years old.
7a. What do you think of the current treatments and care available for molybdenum cofactor deficiency type A on the NHS?	Current treatment options on the NHS for babies born with MoCD type A are very poor. There isn't anything currently available that enables them to grow up with the disorder. Diagnostic processes are currently also not good enough. My son got diagnosed by chance because a lab technician decided to run a certain test. Maternity wards should have sulfite dipstick tests for every newborn child to avoid delayed or chance diagnoses.
7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Within the community, I know of several families whose child was diagnosed too late to initiate treatment with cPMP. Many of these children have since passed away, which demonstrates that the current supportive care available simply isn't good enough and others in the community would most definitely agree with me on that. Since outcomes look so incredibly different depending on whether or not your child receives cPMP treatment, there can also be difficulty within the community. It can feel like you can't share your experience because it may upset others who weren't offered cPMP.
8. If there are disadvantages for patients of current NHS treatments for molybdenum cofactor deficiency type A (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I cannot speak on this from personal experience.
9a. If there are advantages of fosdenopterin over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	My son is still here. If he had received current treatments available on the NHS, he would no longer have been here and he wouldn't have grown up to be the child he is today. He has not experienced any progression of the disease, his biochemistry levels are completely normal. Doctors and school are happy with him. He is progressing as expected. He is part of our family like our other children and growing up with his peers like we would have expected.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	The most important advantage is that he is still here today and can be part of family life like our other children.
9c. Does fosdenopterin help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	N/A
10. If there are disadvantages of fosdenopterin over current treatments on the NHS please describe these. For example, are there any risks with fosdenopterin? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Any and all limitations of cPMP are outweighed by its benefits. The main limitation is the requirement to freeze cPMP in a medical grade freezer which limits our ability to travel as a family. My son has never had side effects to the treatment. He does get a sunburn very easily and we do not know if this is related to treatment or to the fairness of his skin. His central line can also be a drawback as it can be sensitive and needs to be protected from e.g. water.
11. Are there any groups of patients who might benefit more from fosdenopterin or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Ideally every child with MoCD type A is offered this treatment. cPMP should not be taken away from anyone irrespective of whether they have experienced progression.
12. Are there any potential equality issues that should be taken into account when considering molybdenum cofactor deficiency type A and fosdenopterin? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	N/A

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	N/A

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: **Uncertainties related to non-randomised evidence and small sample size**	
Key Issue 2: **Inconsistency of numbers included in the clinical inputs to the economic model**	
Key Issue 3:	See responses to other sections. Briefly, my son's quality of life is exactly the same as any other child. He goes to mainstream school. He is in school full-time. He feeds himself. We have no issues with fluids or drinking. He does have issues with his bowels which is not related to his MoCD type A. Other than that,

Evidence for health-related quality of life from clinical evidence We consider patient perspectives may particularly help to address this issue. Please describe the impact of molybdenum cofactor deficiency type A on your quality of life.	he does everything. He goes swimming three times a week, goes to beaver and local holidays. The only limitation is that he needs to keep his line protected and needs to receive daily treatment. Other than that, I let him do everything. He has always been developmentally delayed, between 12 and 18 months behind his peers, but that does not stop him doing things. He has inclusive education that is tailored to him. He is doing exactly the same in ways that he can do it. He is non-verbal but communicates using an AAC device and Makaton. Though he is now starting to say words.
Key Issue 4: **Intended use in presumptive rather than solely confirmed molybdenum cofactor deficiency**	
Key Issue 5: **Use of fosdenopterin in the late-onset molybdenum cofactor deficiency type A population**	
Key Issue 6: **Extrapolation of fosdenopterin overall survival data**	
Key Issue 7:	See key issue 3

Patient expert statement

Trajectory of quality of life for fosdenopterin patients We consider patient perspectives may particularly help to address this issue. Please describe the expected impact of treatment with fosdenopterin on your quality of life.	
Key Issue 8: **The alleviation of caregiver burden** We consider patient perspectives may particularly help to address this issue. Please describe the expected impact of treatment with fosdenopterin on reducing your caregiver's burden (if applicable).	See responses to other sections. Briefly, if my son had not received cPMP, he would not be here anymore now. There are aspects of our life which are impacted, for example, I have to give him his medication every morning. However, this has become routine practice for us. Additionally, I wasn't working when he was born and took a long hiatus. My son was about 5 years old before I started work again. I have left work since then because it was too much working long hours and looking after my family. I don't have a social life; I cannot go out in the evening as I need to be there to give my son medication in the morning. I do now make sure I have those allowances during the day when my son is at school, doing my hobbies and seeing friends then. We did have one community nurse visit at the beginning when we first came home, but that wasn't for us. We wanted to find our own routine. We also used to receive support from a local hospice, not for overnight stays, but music therapy and events. They were a great resource to find out about financial help, as well as meet other families.

Key Issue 9: **Vial wastage**	The vial wastage changes continuously. At the moment, we have minimal vial wastage, but once he gets a little bit bigger, we will have to open up a third vial and expect to initially waste quite a bit of that. Only once he stops growing will we know what his long-term dosage needs are and how much of a vial we waste. In the past, we used a different formulation of cPMP that was frozen. We saw a lot more wastage with that, as the vials were a lot larger, about 15ml per vial. It also needed a pump to push it through his line, which meant extra equipment. Now we can manually push the medication through.
Key Issue 10: **The ability of the cost-effectiveness model to reflect a patient's experience of molybdenum cofactor deficiency type A** We consider patient perspectives may particularly help to address this issue. Please describe the expected impact of treatment with fosdenopterin on symptoms of molybdenum cofactor deficiency type A, including seizure and	See responses to other sections. Briefly, my son does not have any MoCD type A symptoms. He has never had seizures, never had any medication for seizures and is able to feed himself. The excessive startle reflex he had as a newborn disappeared within 12 hours. In the clinical trial, I do not believe his mild learning disability was captured and it is still unclear whether him being non-verbal is MoCD type A related or not.

the ability to receive food through the mouth.	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- cPMP (fosdenopterin) should be made available to everyone with MoCD type A.
- Routine testing should be in place for MoCD type A to avoid newborn babies going undiagnosed.
- cPMP has the potential to allow children with MoCD type A to grow up beyond an age previously considered possible, live a normal life and be part of society.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

Fosdenopterin for Molybdenum cofactor deficiency (type a) [ID6264]

A Highly Specialised Technology Appraisal

EAG response to Technical Engagement Updated

July, 2024

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
Authors	**Maxwell S. Barnish**[1] **Ollie Hale**[1,2] **Will Battershill**[1,2] **Sophie Robinson**[1] **Ash Bullement**[1,2] **Jessica Owen**[1,2] **Srividya Sreekantam**[3] **G.J. Melendez-Torres**[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [2] Delta Hat Ltd, Nottingham [3] Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK
Correspondence to	Dr Maxwell S. Barnish 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk
Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR 136273.
Declared competing interests of the authors	None.

This addendum is linked to: Barnish MS, et al. Fosdenopterin for Molybdenum cofactor deficiency (type a) [ID6264]. Peninsula Technology Assessment Group (PenTAG), 2024.

1. INTRODUCTION

The purpose of this addendum is to provide updated post-Technical Engagement cost-effectiveness results, in light of the company's revised PAS.

2. REVISED COST-EFFECTIVENESS RESULTS

The EAG has revised the results of its exploratory analyses and base case cost-effectiveness analysis to account for the new patient access scheme (PAS) discount agreed by the company with NHS England. The PAS discount has been increased from [redacted] to [redacted].

Following technical engagement, the company and external assessment group (EAG) base cases were aligned for a number of settings, the EAG preferred settings now included in the company base case are:

- All of the technical corrections made by the EAG have been included
- Using the exponential parametric survival model for the overall survival of fosdenopterin
- Using the utility value for adult Dravet syndrome patients for adult MoCD Type A patients
- Linearly interpolating weight data for patients aged 16-25 years old

This resulted in a company base case incremental cost-effectiveness ratio (ICER) of £[redacted]/QALY when accounting for the updated PAS discount. The results in

Table 1 are an update of Table 26 in Section 6.2 of the original EAG report, which reported the exploratory scenarios conducted by the EAG.

Table 1: EAG exploratory analyses with revised PAS

Scenario description	EAG report section(s)	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	Δ post-TE company base case (£/QALY)
Company post-TE base case		[redacted]	12.38	[redacted]	
Early-onset MoCD Type A population	**Error! Reference source not found.**	[redacted]	12.88	[redacted]	[redacted]
Fosdenopterin patients have a utility halfway between SOC patients and general population	**Error! Reference source not found.**	[redacted]	8.48	[redacted]	[redacted]
Time to non-oral feeding to differentiate fosdenopterin patients	**Error! Reference source not found.**, **Error! Reference**	[redacted]	5.89	[redacted]	[redacted]

Scenario description	EAG report section(s)	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	Δ post-TE company base case (£/QALY)
	source not found.				
Patients receive more than one anti-seizure medication	**Error! Reference source not found.**	[redacted]	12.38	[redacted]	[redacted]
SOC patients do not visit metabolic physicians	**Error! Reference source not found.**	[redacted]	12.38	[redacted]	[redacted]

Key: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MoCD, molybdenum cofactor deficiency; QALY, quality-adjusted life year; SOC, standard of care; TE, technical engagement.

Table 2 presents the development of the ICER from the company post-technical engagement base case to the EAG base case, which remains unchanged in its settings. The deterministic ICER was previously £[redacted] per QALY, with the updated PAS discount this has decreased to £[redacted] per QALY.

Table 2: EAG base case analysis with revised PAS

Preferred assumption	EAG report section(s)	Cumulative ICER £/QALY
Company post-TE base case		[redacted]
Early-onset MoCD Type A population	**Error! Reference source not found.**	[redacted]
Patient weight is modelled using 25th percentile data	**Error! Reference source not found.**	[redacted]
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Time to non-oral feeding to differentiate fosdenopterin patients	**Error! Reference source not found.** and **Error! Reference source not found.**	[redacted]
EAG preferred deterministic ICER incorporating all of the above changes		[redacted]
EAG preferred probabilistic ICER incorporating all of the above changes		[redacted]

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As part of technical engagement, the company presented a scenario using seizure rates to derive utility values. Both the company and EAG agree this scenario has its limitations and should not be used in the base case analysis, nevertheless it is a useful analysis for the committee's consideration. The EAG made a correction to the methodology employed in this scenario to use a weighted average utility, rather than using the utility aligned with the average number of seizures per day in each arm. Results using both the company and EAG method, with the latest PAS discount, are presented in Table 3.

Table 3: Scenario using seizures per day to derive patient utility

Approach to average utility by seizure count	Inc. costs (£) versus SOC	Inc. QALYs versus SOC	ICER (£/QALY) versus SOC
Company absolute average seizure count	[redacted]	[redacted]	[redacted]
EAG weight average of seizure related utilities	[redacted]	[redacted]	[redacted]

Key: EAG, external assessment group; Inc., incremental; QALY, quality-adjusted life year; SOC, standard of care.

3. BRIDGING THERAPY

[redacted]

The cost-effectiveness model already captures the cost of treating patients with confirmed diagnoses from birth. To capture the full cost of bridging therapy for presumptive patients the model must also account for the cost of providing fosdenopterin to patients that have a presumptive diagnosis but a genetic test shows do not have MoCD Type A. The number of people initially erroneously diagnosed as having MoCD Type A is not known, which means estimating the totalty cost of 'bridging therapy' difficult. There is also the possibility that the rate of presumptive MoCD Type A diagnosis could increase once a treatment is made available that provides benefit to patients but must be provided quickly. As a result, the EAG cannot provide a singular impact of bridging therapy on the cost-effectiveness of fosdenopterin. Instead, a two-way analysis has been conducted that varies the length of bridging therapy and the false diagnosis rate to understand the impact on cost-effectiveness. [redacted]

Table 4: Impact of NHS funding bridging therapy on cost-effectiveness (ICER and change from EAG base case)

	False presumptive diagnosis rate				
	10%	**25%**	**50%**	**75%**	**95%**
7 days bridging therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28 days bridging therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

If fosdenopterin were to be considered cost-effective the scenario where the NHS also funds any bridging therapy is unlikely to impact the cost-effectiveness of the product. The duration of bridging therapy relative to the lifetime duration of treatment makes it a very low proportion of the total treatment cost.

Fosdenopterin for Molybdenum cofactor deficiency (type a) [ID6264]

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Key: EAG, external assessment group; Inc., incremental; QALY, quality-adjusted life year; SOC, standard of care.

3. BRIDGING THERAPY

In their dossier the company proposes providing 'bridging' therapy to patients with a presumptive diagnosis until the diagnosis is confirmed using a genetic test. The bridging therapy would allow for the provision of fosdenopterin to patients with a presumptive diagnosis for up to 28 days at no cost to the NHS. The additional analysis reported in this section explores the impact of this bridging therapy not being provided by the company free of charge and its implications for fosdenopterin's cost-effectiveness.

The cost-effectiveness model already captures the cost of treating patients with confirmed diagnoses from birth. To capture the full cost of bridging therapy for presumptive patients the model must also account for the cost of providing fosdenopterin to patients that have a presumptive diagnosis but a genetic test shows do not have MoCD Type A. The number of people initially erroneously diagnosed as having MoCD Type A is not known, which means estimating the totalty cost of 'bridging therapy' difficult. There is also the possibility that the rate of presumptive MoCD Type A diagnosis could increase once a treatment is made available that provides benefit to patients but must be provided quickly. As a result, the EAG cannot provide a singular impact of bridging therapy on the cost-effectiveness of fosdenopterin. Instead, a two-way analysis has been conducted that varies the length of bridging therapy and the false diagnosis rate to understand the impact on cost-effectiveness. The company suggest that up to 28 days of bridging therapy can be provided, we have also explored the cost of 7 days bridging therapy.

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	False presumptive diagnosis rate				
	10%	**25%**	**50%**	**75%**	**95%**
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If fosdenopterin were to be considered cost-effective the scenario where the NHS also funds any bridging therapy is unlikely to impact the cost-effectiveness of the product. The duration of bridging therapy relative to the lifetime duration of treatment makes it a very low proportion of t