NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# February 2023

## Fosdenopterin for molybdenum cofactor deficiency type A

| Company/Developer | Sentynl Therapeutics |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 9955 | NICE TSID: 9684 | UKPS ID: Not available |
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## Licensing and Market Availability Plans

Currently in phase II and III clinical development.

## Summary

Fosdenopterin is currently in clinical development for the treatment of paediatric patients aged 1 day to 5 years with molybdenum cofactor deficiency (MoCD) type A. Patients with MoCD type A cannot produce a substance known as cyclic pyranopterin monophosphate (cPMP). MoCD type A is a rare genetic disease that can appear shortly after birth and is caused by the mutation of the MOCS1 gene in the body. This leads to the deficiency of certain compounds and enzymes such as sulfite oxidase (SOX) and without these enzymes, the toxic chemical sulfite can build-up in the brain. This leads to symptoms such as seizures (fits), severe brain abnormalities, bleeding in the brain, increased reflex responses and feeding problems, alongside the severity and poor survival associated with the condition. Patients with MoCD type A who survive beyond infancy typically suffer from progressive brain damage, and an inability to make coordinated movements or communicate with their environment. Currently there are no licensed or recommended therapies available for patients with MoCD in the UK.

Fosdenopterin is a substance that replaces cPMP in patients with MoCD type A. The body then uses this substance to produce molybdenum cofactor, allowing it to start producing molybdenum-dependent enzymes and reducing the levels of sulfite accumulation in the brain. If licensed, fosdenopterin would offer a novel treatment option for affected children.

## Proposed Indication

For the treatment of patients with molybdenum cofactor deficiency (MoCD) type A.[1]

# Technology

## Description

Fosdenopterin (Nulibry; ORGN001, ALXN1101) is a synthetic form of cyclic pyranopterin monophosphate (cPMP) used as a replacement substrate in patients with molybdenum cofactor deficiency (MoCD) type A.[1,2] Patients with MoCD type A have mutations in the Molybdenum Cofactor Synthesis 1 (*MOCS1*) gene leading to deficient *MOCS1*A/B dependent synthesis of the intermediate substrate, cPMP.[3] Fosdenopterin replaces an intermediate substrate in the synthesis of molybdenum cofactor, a compound necessary for the activation of several molybdenum-dependent enzymes including sulfite oxidase (SOX).[2,4] The loss of SOX activity appears to be the main driver of MoCD morbidity and mortality, as the build-up of neurotoxic sulfites typically processed by SOX results in rapid and progressive neurological damage.[2] Given that SOX is responsible for detoxifying sulfur-containing acids and sulfites such as S-sulfocysteine (SSC), urinary levels of SSC can be used as a surrogate marker of efficacy for fosdenopterin.[2,5]

Fosdenopterin's clinical development program includes neonates, infants and children with MoCD type A.[1] Fosdenopterin is administered as an intravenous infusion. The recommended dose is 0.90 mg per kilogram body weight. For patients less than one year of age a lower starting dose and titration schedule are recommended. The starting dose and titration schedule depend on the gestational age at birth. Treatment needs to be continued for life if the condition is confirmed by genetic testing.[3]

## Key Innovation

MoCD is an ultra-rare genetic disease that remained untreatable until the recent introduction of cPMP substitution.[6] Studies in a mouse model showed the benefit of replacement of cPMP, a precursor of the cofactor lacking in two-thirds of patients with MoCD.[7] In the results of a recent study, cPMP substitution has shown signs of the first effective therapy for patients with MoCD type A and has a favourable safety profile. The study results also show restoration of molybdenum cofactor-dependent enzyme activities results in a greatly improved neurodevelopmental outcome when started sufficiently early.[8] If licensed, fosdenopterin will provide a treatment option for patients with MoCD type A.

## Regulatory & Development Status

Fosdenopterin does not currently have marketing authorisation in the UK for any indication.

Fosdenopterin is indicated in the EU for the treatment of patients with MoCD type A.[9]

Fosdenopterin has the following regulatory designations/awards;[10,11]

- an orphan drug in the EU in September 2010 for MoCD
- a breakthrough therapy by the US FDA MoCD in February 2021

# Patient Group

## Disease Area and Clinical Need

MoCD is a rare autosomal-recessive disorder in which patients are deficient in three molybdenum-dependent enzymes: SOX, xanthine dehydrogenase, and aldehyde dehydrogenase.[2,4] Without these enzymes, the toxic chemical sulfite builds up in the brain. The most common subtype of MoCD is type A. In the 'type A' form of the disease, the absence of molybdenum cofactor is due to patients lacking a

substance called cyclic pyranopterin monophosphate. The body needs this substance in the synthesis of molybdenum cofactor necessary in the pathway to prevent toxic sulfite accumulation in the brain.[10,12] MoCD represents a spectrum, with some individuals experiencing significant signs and symptoms in the neonatal period and early infancy also known as early-onset or severe MoCD and others developing signs and symptoms in childhood or adulthood also known as late-onset or mild MoCD.[13] The symptoms of MoCD include intractable seizures, intracranial haemorrhage (bleeding in the brain), increased reflex responses and feeding problems, encephalopathy, exaggerated startle reactions, axial hypotonia, limb hypertonia, gross destruction of the brain, failure to thrive, poor or halted feeding response, and high pitch crying.[4,10,14,15] MoCD type A is a very severe and life-threatening condition, which is associated with poor overall survival, with death usually occurring within the first few months of life.[10] Late-onset MoCD is typically characterised by milder symptoms, such as acute neurologic decompensation in the setting of infection. Episodes vary in nature but commonly consist of altered mental status, dystonia, choreoathetosis, ataxia, nystagmus, and fluctuating hypotonia and hypertonia.[13]

MoCD is a rare but devastating metabolic disease. It first appears in the newborn period. It is estimated to affect 1 in 100,000 to 200,000 newborns worldwide.[16,17] In England, in 2021-22, there were 12 admissions with a primary diagnosis of molybdenum deficiency (ICD-10 code E61.5) resulted in 12 finished consultant episodes (FCE), 87 bed days and 5 day cases.[18]

## Recommended Treatment Options

There is currently no recommended treatment option for MoCD Type A.[7] Treatments aimed at relieving the symptoms of the disease, such as using medicines to control seizures, and at providing general support to help care for the patients.[10] Affected individuals are often placed on a cysteine-restricted diet, which typically includes low protein intake with restriction of whole natural protein; in those with MoCD type A.[13]

## Clinical Trial Information

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| Trial | NCT02629393; 2013-002702-30; A Phase 2/3, Multicenter, Multinational, Open Label Study to Evaluate the Efficacy and Safety of ORGN001 (Formerly ALXN1101) in Neonates, Infants and Children With MoCD) Type A<br>**Phase II/III –** Completed<br>**Location(s):** 1 EU country, UK, US and other countries<br>**Completion date:** October 2022 |
| Trial Design | Open label, single assignment |
| Population | N=5 (actual); Neonates and infants with confirmed or suspected MoCD type A. |
| Intervention(s) | Fosdenopterin |
| Comparator(s) | No comparator |
| Outcome(s) | Primary: Overall survival [Time frame: 36 months]<br><br>See trial record for full list of other outcomes |

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| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | NCT02047461; 2013-002701-56; A Phase 2, Multicenter, Multinational, Open Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of ORGN001 (formerly ALXN1101) in Paediatric Patients with MoCD Type A Currently Treated with Recombinant Escherichia Coli-Derived Cyclic Pyranopterin Monophosphate (rcPMP)<br>**Phase II –** Completed<br>**Location(s):** UK, US, Australia, Tunisia, and the Netherlands |
| Trial Design | Open label, single assignment, dose-escalation study |
| Population | Patients with MoCD type A who were receiving treatment with rcPMP. |
| Intervention(s) | Fosdenopterin |
| Comparator(s) | No comparator |
| Outcome(s) | To evaluate the safety of fosdenopterin over the first 6 months of treatment.<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | NCT01735188; A natural history study of Molybdenum Cofactor and Isolated Sulphite Oxidase Deficiencies<br>**Location(s):** 5 EU countries, UK, US and other countries<br>**Completion date:** June 2016 |
| Trial Design | Retrospective and Prospective Natural History Study, Multinational, Multicenter |
| Population | Patients with isolated SOX deficiency |
| Intervention(s) | None – natural history study |
| Comparator(s) | None – natural history study |
| Outcome(s) | To characterise the natural history of MoCD type A, the most common subtype of MoCD, in terms of survival [Time Frame: 12 months] |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | NCT01640717; A Retrospective, Observational, Noninterventional Data Collection Study for Patients with MoCD who have previously been treated with Cyclic Pyranopterin Monophosphate (cPMP)<br>**Non-interventional** – Completed<br>**Location(s):** 2 EU countries, UK, US, Australia and Turkey<br>**Completion date:** October 2014 |
| Trial Design | Retrospective, non-interventional, observational |
| Population | Paediatric patients with MoCD type A, B, and unknown |
| Intervention(s) | None |
| Comparator(s) | None |
| Outcome(s) | Safety and Efficacy [Time Frame: For up to 60 months from the initial date of treatment with cPMP] |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of fosdenopterin is not yet known.

## Relevant Guidance

### NICE Guidance

No relevant guidance identified

### NHS England (Policy/Commissioning) Guidance

No relevant guidance identified

### Other Guidance

No relevant guidance identified

## Additional Information

Sentynl Therapeutics did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

# References


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