Fosdenopterin for treating molybdenum cofactor deficiency type A

For PUBLIC –
CON information redacted [redacted]

Highly specialised technologies evaluation committee 15 August 2024

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Fosdenopterin for treating molybdenum cofactor deficiency type A

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Cost-effectiveness results
- ❑ Other considerations
- ❑ Summary

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Background on molybdenum cofactor deficiency type A (1/2)

MoCD type A is a rare genetic condition with poor survival outcome

Further background

Description and causes

- Rare genetic condition that can appear shortly after birth → 73% within the first 28 days of life
- Caused by (pathogenic) defects in the *MOCS1* gene – which makes molybdenum cofactor
- Without molybdenum cofactor, sulfite-oxidase does not function properly to process sulfites
- Build-up of sulfites in the brain causes rapid and irreversible neuron and brain damage

Epidemiology

- Prevalence estimated to be less than 1 in 100,000 – 200,000
- Only 53 cases have been reported in the EU

Diagnosis

- Suspected MoCD is confirmed by genetic test of *MOCS1* in a hospital

MoCD, molybdenum cofactor deficiency; MOCS1, molybdenum cofactor synthesis 1; EU, European union

Background on molybdenum cofactor deficiency type A (2/2)

MoCD type A is a rare genetic condition with poor survival outcome

Further background

Classification

- Early onset: within first month of life
  - more severe form
  - typical symptoms→ seizure, feeding difficulty, paralysis
- Late onset: within 2 years of life
  - typical symptoms→ developmental delay, (eye) lens discolouration, involuntary movement

Prognosis

- Median survival: 4 years
- Clinical advice suggests people who have treatment early and before brain damage have better prognosis

MoCD, molybdenum cofactor deficiency; MOCS1, molybdenum cofactor synthesis 1; EU, European union

Impact of MoCD type A on children

Affects many aspects of the daily life of children

Submissions from Metabolic Support UK

Medication

- require numerous medicines given throughout the day to control seizure and muscle movements

Feeding

- require fitting of nasogastric tube to have food

Irritability

- severe brain damage can cause irritability

Seizure

- people tend to have multiple seizures a day (up to 60 times daily)

Healthcare visits

- frequent multiple unplanned visits are common, can involve long travelling to specialist centres

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"requirement to freeze fosdenopterin in a medical grade freezer …limits our ability to travel as a family"

"first year was definitely the hardest as he did require a lot more comforting and was often inconsolable"

"[in my case], my son has never had any medication for seizures and is able to feed himself"

MoCD, molybdenum cofactor deficiency

Patient carer perspectives

Life-limiting disease which has a significant impact on carers

Submissions from Metabolic Support UK

- A progressive, life-limiting diseases that reduces life expectancy
- Parents have to adjust their entire lives to becoming full time carers and learning how to give treatments needed throughout the day

  →has a profound impact on parents

  →parent report feelings such as anxiety, worry, and frustration
- Over time, families may experience that seizure medicines no longer work or that the dose needs to be changed
- Families who received fosdenopterin before irreversible brain damage reported positive impact

  →early treatment important

"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"

"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…"

Clinical perspectives

No available treatments, current medicines aim to manage symptoms

Submissions from clinical expert

- A high unmet need because there is no other causal treatment or defined pathway for MoCD type A

  →current management focus on symptoms: antiseizure medicines and tube feeding for swallowing difficulty

- Treatment has potential to prevent people with MoCD Type A from having severe neurodisability
- Some treatment benefits are difficult to capture by typical questionnaires

  →eye and kidney complications

- Early diagnosis and initiation of fosdenopterin treatment is key to changing the outcomes of babies born with MoCD type A
- Balanced clinical decision needed to stop fosdenopterin in people who have a biochemical response but also have evidence of brain damage

"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."

MoCD, molybdenum cofactor deficiency

Equality considerations

Company

- No equality issues with the introduction of fosdenopterin to clinical practice
- Recommending fosdenopterin could reduce carer burden, caring tends to be disproportionally done by women

Clinical expert

- Almost all known UK patients come from minority ethnic groups

  →high incidence in people from South Asian family background

EAG clinical expert : linked with consanguinity rather than with being South Asian

Metabolic Support UK

- More common in people from consanguineous family background, this should be considered
- Families with low income may not have access to medical grade freezer needed to store fosdenopterin

Evidence for improved benefit for specific groups not submitted by company

Fosdenopterin (Nulibry, Sentynl Therapeutics)

Marketing authorisation	• 'for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A' • only if the person has a **confirmed genetic** or **presumptive** diagnosis • UK MA granted April 2024
Mechanism of action	• Acts as external source of cPMP, which is converted to molybdenum cofactor (MoCo) • MoCo is needed for activating enzymes that reduce toxic levels of sulfites
Administration	• By intravenous infusion • Detailed dosage information based on age available in the SmPC • Treatment stopped if test negative otherwise lifelong treatment
Price	• £1,205.51 per 9.5mg vial • Year 1 treatment cost with list price : £529,158 per person per year • Year 5 treatment cost with list price: £1,056,748 per person per year (takes weight into account) • PAS discount in place for fosdenopterin

EAG: substantial amount of treatment wasted due to vial size and storage requirement

[Treatment wastage]

NICE

MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; cPMP, cyclic pyranopterin monophosphate; SmPC, summary of product characteristic; PAS, patient access scheme

Treatment pathway

Fosdenopterin is given presumptively before confirmation of MoCD type A

List of SOC medicines

Phenytoin
Nitrazepam
Levetiracetam
Lorazepam
Diazepam
Clonazepam
Pyridoxine
Valproate sodium
Midazolam
Phenobarbital

Clinical presentation of MoCD and evidence of sulfite build-up

Note:
- Presumptive diagnosis

Start fosdenopterin immediately and do confirmatory genetic diagnostic tests

Note:
- Fosdenopterin is used with SOC:
  - **Antiseizure medicines**
  - **Dietary changes**
  - **Feeding tube**
- It is a life-long treatment

If tests confirm MoCD type A continue fosdenopterin

If tests do not confirm MoCD type A stop fosdenopterin

- Does this reflect the treatment pathway for fosdenopterin?
- What is considered SOC for people with MoCD type A?
- How is treatment confirmation done in clinical practice?

MoCD, molybdenum cofactor deficiency; SOC, standard of care

Key issues

Issue	Resolved?	ICER impact
Are the fosdenopterin trials suitable for decision-making?	No – to discuss	Unknown
• What is the appropriate population to apply in the model? • Does the clinical trial data sufficiently capture people with early- and late-onset MoCD type A?	No – to discuss	Large
Is it appropriate to apply proxy quality of life data (from Dravet syndrome)?	No – to discuss	Unknown
•Does the model capture the relevant MoCD type A outcomes? •Are people with MoCD type A expected to have general population outcomes after treatment for 1 year? •Should seizure or feeding status be used to differentiate outcomes in the model?	No – to discuss	Large
• Which carer burden assumption is plausible – EAG or company? • Are people with MoCD type A likely to require care beyond age 5?	No – to discuss	Large
Should the cost of presumptive treatment be captured in the model?	No – to discuss	Small
What is the committee's view on fosdenopterin's wastage?	No – to discuss	Unknown
What is the most appropriate data cut to use for the clinical and economic analysis?	Partially	Unknown
What is the correct model for extrapolating survival?	Yes	Large

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Key clinical trials

Clinical trial designs and outcomes

Company:
- fosdenopterin referred to as cPMP
- rcPMP and cPMP are equivalent

	MCD-501 (N=4)	MCD-201 (N=8)	MCD-202 (N=3)	MCD-502 (N=37)
Design	Retrospective, observational	Phase 2, open-label	Phase 2/3, open-label	Natural history, retrospective and prospective
Population	Patients with MoCD Type A previously treated with rcPMP	Patients with MoCD Type A currently treated with rcPMP	Paediatric patients up to 5 years with confirmed or suspected MoCD Type A	Patients with MoCD Type A
Intervention	rcPMP	cPMP	cPMP	Natural history
Comparator(s)	N/A	N/A	N/A	N/A
Outcomes	Included survival, feeding and growth pattern, and seizure frequency			
Locations	Global including UK			
Used in model?	Yes, pooled fosdenopterin results			

FAS: all people treated and untreated
GMAS: treated people genotype-matched to untreated

EAG:
•fosdenopterin trials are all single-arm trials

MoCD, molybdenum cofactor deficiency; cPMP, cyclic pyranopterin monophosphate; rcPMP, recombinant cyclic pyranopterin monophosphate; N/A, not applicable; FAS, full analysis set; GMAS, genotype-matched analysis set

Key issue: Size and nature of trials

ICER impact: unknown

Link to urinary biomarker results

Background

- All fosdenopterin trials are single-arm trials
- Total population across trials is small despite pooling the studies
  →Fosdenopterin (N=15), SOC (N=37)

EAG comments

- Increased uncertainty in the clinical results and cost-effectiveness estimates
- Acknowledge issue intrinsic to the MoCD type A population

Company response to TE

- Measures were taken to minimise bias and ensure comparability:
  - use of objective outcomes (survival and reduction of s-sulphocysteine levels)
  - matching of treated population with external control based on genotype

Clinical expert

- Issue inherent in all rare diseases
- Weakness in the data would not be overcome with a different methodological approach
- Randomisation unlikely to address heterogeneity in population and outcomes

MoCD, molybdenum cofactor deficiency; TE, technical engagement

Are the fosdenopterin trials suitable for decision-making?

Baseline characteristics in fosdenopterin trials

Baseline characteristics for the integrated efficacy analysis

	Fosdenopterin (n=15)	SOC	
		(FAS, n=37)	(GMAS, 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%)

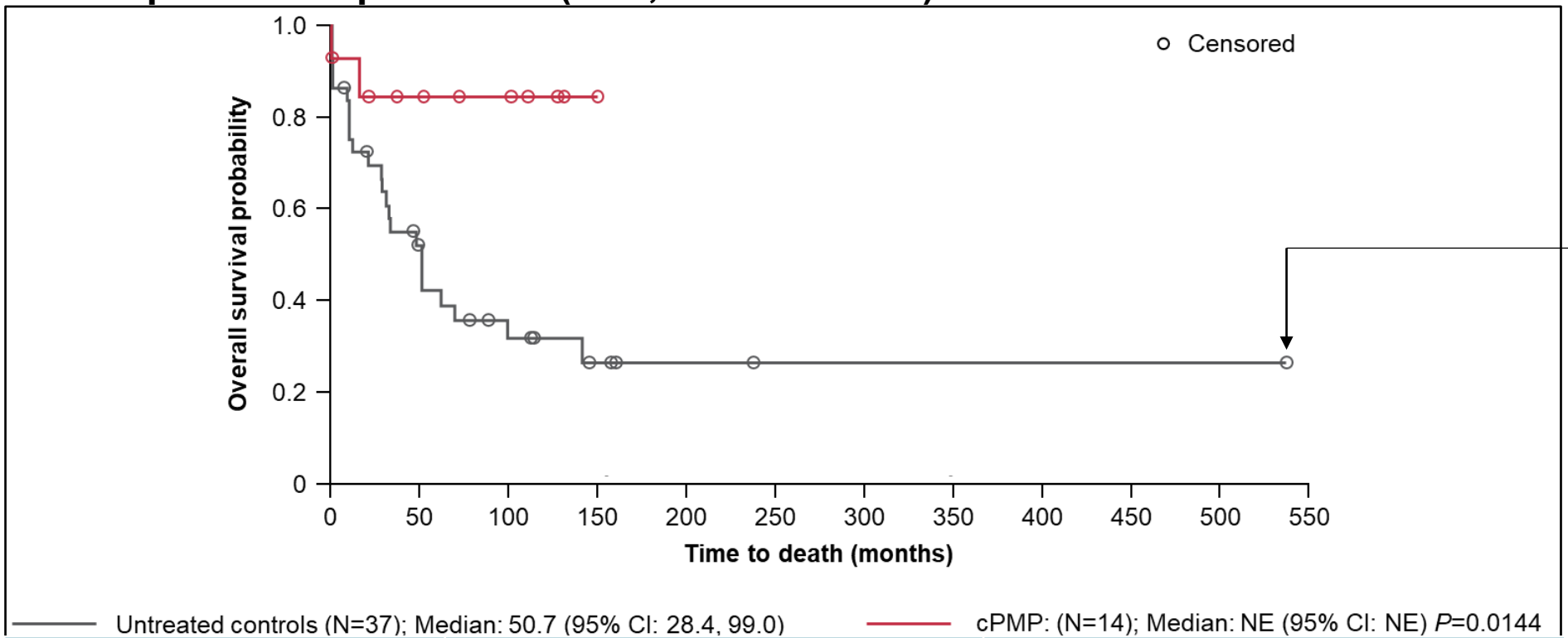
EAG: one person in the SOC group was diagnosed at age 40 (month 484)

NICE Are these baseline characteristics generalisable to NHS clinical practice?

FAS, full analysis set; GMAS, genotype-matched analysis set; SD, standard deviation; MoCD, molybdenum cofactor deficiency; SOC, standard of care

Key clinical trial results: overall survival

Kaplan-Meier plot of OS (FAS, October 2021)



	FAS		GMAS	
	Fosdenopterin	SOC	Fosdenopterin	SOC
Median OS (months)	NE	50.7	NE	47.8
HR (95 % CI)	5.5 (1.44, 21.04)		7.1 (NR)	
Alive at				
12 months (%)	93	75	93	68
24 months (%)	86	70	85	63
36 months (%)	86	55	86	52

Does censoring markedly impact the results?

Company pooled trial results

EAG: Person was diagnosed at month 484, had same risk as general population before diagnosis

	FOS (N=15)	SOC (N=37)
Censored, n (%)	13 (86.7)	13 (35.1)
Reason for censoring, n (%)		
Data cut-off	10 (66.7)	0
Alive at last contact	3 (20)	13 (35.1)
Deaths	2 (13.3)	24 (64.9)

cPMP, cyclic pyranopterin monophosphate; FAS, full analysis set; NE, not estimable; NR, not reported; FAS, full analysis set; GMAS, genotype-matched analysis set; FOS, fosdenopterin; SOC, standard of care

Key clinical trial results: seizure control

More people treated with fosdenopterin had their seizure resolved

Seizure status at last assessment (FAS and GMAS, 2022)

EAG: no statistical significance

	Fosdenopterin				SOC	
	MCD-501 only	MCD-201	MCD-202	Total	MCD-502 FAS	MCD-502 GMAS
	(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*	-	-	-	1.216		1.461
(95% CI)				(0.337, 4.387)		(0.368, 5.808)

*Odds of Not Present or Resolved versus Controlled or Present; for treated vs natural history population
†Some people in MCD-501 also included in study MCD-201

Not present: never had seizures
Resolved: had seizures, but have resolved (without anti-seizure medication)
Controlled: had seizures, and are now controlled with the use of anti-seizure medications, defined as no reported seizures in the past 6 months
Present: still having seizures regularly defined as > 1 seizure in the past 6 months

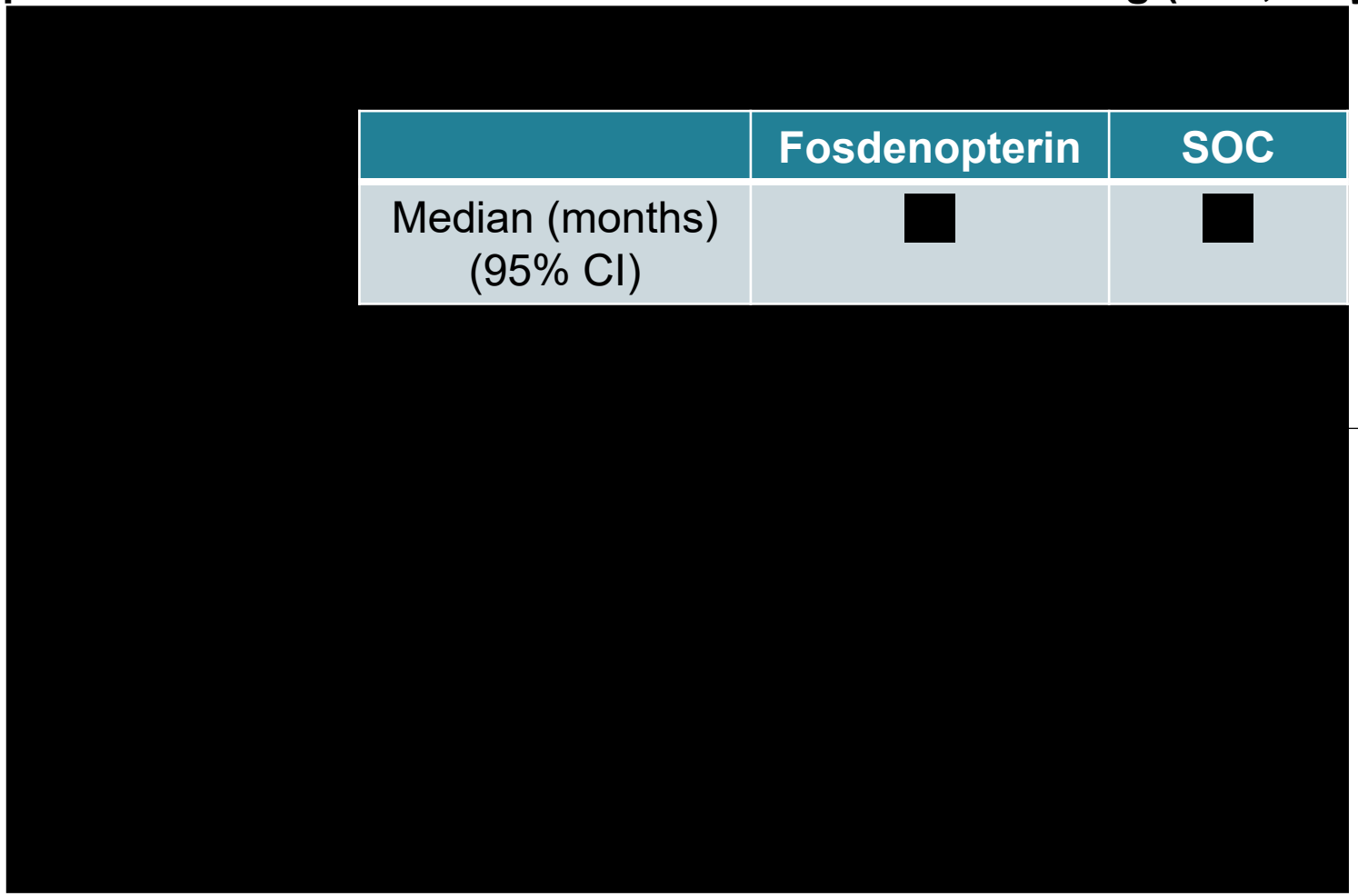
Seizure data not included in company base case

cPMP, cyclic pyranopterin monophosphate; FAS, full analysis set; GMAS, genotype-matched analysis set; SOC, standard of care

Key clinical trial results: non-oral feeding

Fosdenopterin increased the time to sustained non-oral feeding

Kaplan-Meier curves of time to sustained non-oral feeding (FAS, July 2019)



	Fosdenopterin	SOC
Median (months) (95% CI)	[redacted]	[redacted]

Non-oral feeding includes the use of nasogastric feeding tubes

EAG: Person was diagnosed at month 484, had same risk as general population before diagnosis

FAS, full analysis set; NE, not estimated; SOC, standard of care

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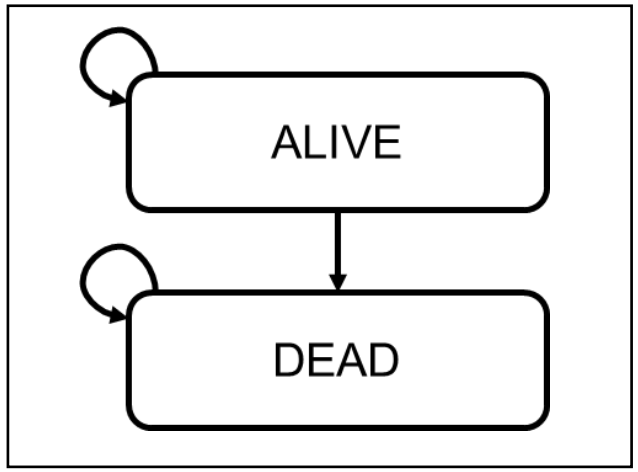
Company's model overview

Model structure



- Technology affects **costs** by:
  - Adding the acquisition cost of fosdenopterin
  - Increasing survival and in turn increasing management cost
  - Reducing the prevalence of non-oral feeding
- Technology affects **QALYs** by:
  - Reducing the mortality rate of MoCD Type A
  - Reducing the burden on care givers
- Assumptions with greatest ICER effect:
  - Model used to extrapolate overall survival data
  - Utility that people experience while having fosdenopterin
  - Long-term care giver requirements for people receiving fosdenopterin

Cycle length: 4 weeks
Time horizon: up to 100 years
Utility source: Proxy, caregiver completed EQ-5D-5L for Dravet syndrome

How company incorporated evidence into model

Company base case	EAG base case
Assumption: people on fosdenopterin and alive after 1 year have similar outcomes to general population including utilities, feeding ability and survival	**Structure:** oral feeding as a proxy for outcomes: only people feeding orally have similar outcomes to general population

- What is the appropriate model structure for MoCD type A?
- Is the company's model appropriate for decision making?

QALYs, quality-adjusted life year; MoCD, molybdenum cofactor deficiency

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Key Issue: Appropriate treatment population (1/2)

ICER impact: Large

Company and EAG disagree on model population

Background

- Company defined early-onset as people with symptoms within 28 days of birth
- Fosdenopterin considered for all people with MoCD type A, that is, both early- and late-onset
- In the company model, most people in the fosdenopterin (n=14/15) and SOC group (n=33/37) had early-onset MoCD type A

EAG comments

- Data for single late-onset person (n=1/15) treated with fosdenopterin did not impact model
- More late-onset data needed to be able to model this group
- EAG base case uses early-onset data only
- Early-onset group have worse outcomes, applying this reduces survival for the SOC arm

Company response to TE

- New evidence (Lund et al., 2024) supports similar rapid clinical improvement for people with late-onset disease
- People with late-onset disease have less brain damage and likely respond better to treatment
- Trial with more people with late-onset disease not feasible due to small population

MoCD, molybdenum cofactor deficiency; TE, technical engagement; SOC, standard of care

Lund et. al study

Key Issue: Appropriate treatment population (2/2)

ICER impact: Large

Company and EAG disagree on model population

EAG critique of company response to TE

- Lund et al. provides evidence that fosdenopterin could be used for late-onset MoCD type A
- But no additional data included in the model, model still only reflects early-onset group
- Heterogenous groups:
  →Lund et al. included 2 late onset people diagnosed at age 10 months and 14 months
  →MCD-502 (SOC arm) includes one person diagnosed at age 40 years
- Heterogeneity would impact the results
  →Late diagnosis (at age 40 years) would count as survival in the SOC arm and bias overall survival, important as model is driven by overall survival
- Issue unresolved, EAG maintains its position that model only reflects early-onset group

- Does the clinical trial data sufficiently capture people with early- and late-onset MoCD type A?
- How many people with late-onset MoCD type A would be required to sufficiently model this group?
- What is the appropriate population to apply in the model?
- If more late-onset data were available, is the model structurally able to assess late-onset MoCD type A?

MoCD, molybdenum cofactor deficiency; TE, technical engagement; SOC, standard of care

Key issues: Quality of life data (1/2)

ICER impact: unknown

Background

- Company did not collect health-related quality of life (HRQoL) data in its trials
- Data from Dravet syndrome study (Lagae et al., 2018) was used as a proxy to generate utility values
- Dravet syndrome is a severe form of epilepsy that typically starts during childhood
  →seizures start within first year of life

Summary of Lagae et al., 2018 (source of proxy utility)	
N	584
Location	Europe (including UK)
Population	Paediatric (83%) and adult (17%) patients with Dravet syndrome
Method	**Caregivers completed EQ-5D-5L** as proxy for the person being cared for • visual analogue scale not included

Key issues: Quality of life data (2/2)

ICER impact: unknown

EAG comments

- Proxy utilities may not accurately match quality of life for people with MoCD type A; this increases uncertainty

Company response to TE

- HRQoL study (recommended by the EAG) not feasible in small population
  →there are practical challenges such as rapid worsening of untreated people
- Dravet syndrome reflects another seizure-based condition - likely conservative because people with MoCD type A experience more seizures

Is it appropriate to apply proxy quality of life data (from Dravet syndrome)?

MoCD, molybdenum cofactor deficiency; HRQoL, health-related quality of life; TE, technical engagement

Key Issue: Model's reflection of MoCD type A outcomes (1/3)

ICER impact: Large

EAG made structural changes to the model – oral feeding to define outcomes

Model structure

Background

- Company model based on overall survival outcomes (proposed primary benefit of fosdenopterin)
- Outcomes such as developmental status, nasogastric feeding and seizure not captured → costs included but not health benefits
- Company assumed after treatment with fosdenopterin for 1 year, people with MoCD type A would have the similar survival outcomes, feeding ability and quality of life as the general population

EAG comments

- Oversimplified methodology (based on overall survival) when trying to model a complex disease
- Economic benefit of fosdenopterin to improving specific symptoms cannot be tested in the model
- Company utility assumption not plausible
- EAG used ability to feed orally as proxy for people with similar outcomes to the general population
- People having fosdenopterin **and**
  - → feeding orally have utility midway between SOC and general population
  - → unable to feed orally maintain fosdenopterin survival benefits but have the same quality of life as the SOC population

MoCD, molybdenum cofactor deficiency; SOC, standard of care

Utilities used in company and EAG base case

Key Issue: Model's reflection of MoCD type A outcomes (2/3)

ICER impact: Large

Company explored use of seizure data to define outcomes

Company response to TE

- Model validated by clinician and patient organisation
- People treated early have fewer developmental delay and are more likely to feed orally
- EAG approach disregards other quality of life factors such as seizure
- Non-oral feeding not a key determinant of outcomes and quality of life; related to irreversible brain damage which depends on speed of diagnosis and treatment
- General population utilities expected with early treatment
- Company maintains base case but explored two additional scenarios:
  - people not feeding orally have 75% improvement in quality of life vs SOC
  - quality of life linked to daily number of seizures
- EAG base case and company exploratory scenarios increase uncertainty

Clinical expert

- If treated early, similar quality of life to general population possible
- Not all people need antiseizure treatment

MoCD, molybdenum cofactor deficiency; TE, technical engagement; SOC, standard of care

Key Issue: Model's reflection of MoCD type A outcomes (3/3)

ICER impact: Large

EAG critique of company response to TE

- Company provided seizure data for 8 people who had fosdenopterin and SOC
  →unclear how the 8 people were selected from the list of 11 and 37 respectively
- Company used simple average to calculate seizure per day then applied utilities reported in an epilepsy study (Wester et al., 2021)
  →approach flawed, EAG used weighted approach to obtain mean utility
- Evidence not provided to understand if feeding orally and seizure outcomes are correlated
  →best approach but not implemented in the model by company
- Both EAG (non-oral feeding) and company (seizure) approach suggests people having fosdenopterin have lower utility compared with the general population

- Does the model capture the relevant MoCD outcomes?
- Are people with MoCD type A expected to have general population outcomes after treatment for 1 year?
- Should seizure or feeding status be used to differentiate outcomes in the model?

Distribution of seizure rates in each treatment arm

Daily seizure count	Fosdenopterin	SOC
Seizure-free	38%	0%
1 seizure/day	25%	75%
2-5 seizures/day	38%	13%
6 or more	0%	13%
Mean utility	0.68	0.62

Company seizure results

MoCD, MoCD, molybdenum cofactor deficiency; TE, technical engagement; SOC, standard of care

ICER impact: Large

Key Issue: Carer burden assumption (1/2)

EAG based carer requirement on feeding status

Background

- Company assumed people having SOC need 1.8 carers throughout their life
  →giving care corresponding to 14.8 hours per day
- People having fosdenopterin only need 1 carer until the age of 5 years, none after

EAG comments

- Company did not capture care in institutions such as special needs school
  →should be captured, falls under the scope of personal social service
- Company clinical data shows people still having antiseizure medicine and feeding non-orally – likely to require care beyond age 5
- EAG base case assumes:
  - those feeding orally have better health outcomes, require less care to age 18 and none after
  - those who have non-oral feeding have the same care requirements as the SOC group

Patient organisation (Metabolic Support UK)

- Caregiver survey suggests burden can range from almost none to full-time care

ICER impact: Large

Key Issue: Carer burden assumption (2/2)

Company assumed no carer required with fosdenopterin from age 5

Company response to TE

- Care associated with early treatment is similar to general population after age 5
- Children would not self-administer treatment - expected to fall within regular parenting
- People requiring formalised developmental support would receive this care from sources such as special needs school, this is beyond the scope of a model

Clinical expert

- Treatment administration requires caregiver support
- People who get early treatment can live independently whereas people who get treatment after brain damage require permanent supervision

- Are people with MoCD type A likely to require care beyond age 5?
- Which carer burden assumption is plausible – EAG or company?

TE, technical engagement

Key Issue: Cost of presumptive treatment

ICER impact: Small

Model does not capture full treatment cost

EAG analysis on presumptive costs

Background

- Fosdenopterin can be given presumptively before genetic confirmation of MoCD type A
- Company model does not capture presumptive treatment cost

Company

- Additional cost to the NHS during this period not expected
- Presumptive treatment period not substantial - fosdenopterin is a life-long treatment

EAG comments

- Unclear what number of people who receive treatment presumptively would have a negative genetic test
- Did scenario analysis exploring 10 – 95% of people falsely presumptively diagnosed

Clinical expert

- Severe, irreversible brain damage often occurs within the first few days of birth
- Assessment of treatment response is quick, treatment can be stopped if no response

- Should the cost of presumptive treatment be captured in the model?
- Was presumptive treatment data captured in the clinical trials?

MoCD, molybdenum cofactor deficiency

Summary of company and EAG base case assumptions

*Affects nasogastric feeding cost, utilities, and carer burden

Assumptions in company and EAG base case

EAG and company agree after technical engagement

Assumption	Company base case	EAG base case
Population	Late- and early-onset type A	Early-onset MoCD type A only
Weight	[redacted] percentile	25th percentile
	Age 16-25 linearly interpolated (smoothed)	
Survival model	Individually fitted exponential model for fosdenopterin and SOC	
Time to non-oral feeding*	Not applied	Used as proxy for health in fosdenopterin arm
Utility	Fosdenopterin arm: general population utility after 1-year treatment	Fosdenopterin arm: • Feeding orally- midway between SOC and general population • Non-oral feeding – same as SOC
	Adult utility applied for adults	
Carer burden (no.)	• SOC arm: 1.8 • Fosdenopterin arm: 1 up to age 5, no carer after	Fosdenopterin arm differentiated by time-to non-oral feeding • Feeding non-orally: 1.8 • Feeding orally: 1 until age 18, no carer after
Antiseizure medication (no.)	1	2.2
Metabolic physician for SOC	Yes	No

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QALY weighting for size of benefit

- For HSTs the committee will consider additional weight needed to be assigned to the QALY benefit for the ICER to fall within £100,000/QALY
- For the weighting to be applied there needs to be:
  → compelling evidence that treatment offers significant QALY gains
- Weight between 1 and 3 applied based on incremental QALYs gained

Incremental QALYs gained	Weight
Less than or equal to 10	1
11 to 29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

	Incremental QALYs	
	Discounted	Undiscounted
Company base case	12.38	23.07
EAG base case	5.10	10.05

QALY, quality-adjusted life year

Summary of cost-effectiveness results

Company base case with PAS included

- above the range normally considered cost-effective use of NHS resources regardless of QALY weight applied

EAG base case with PAS included

- above the range normally considered cost-effective use of NHS resources regardless of QALY weight applied

Company base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Undiscounted inc. QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
SOC	[redacted]	14.37	-	-	-	-	-
Fosdenopterin	[redacted]	26.75	[redacted]	12.38	23.07	[redacted]	[redacted]

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Undiscounted inc. QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
SOC	[redacted]	14.43	-	-	-	-	-
Fosdenopterin	[redacted]	26.57	[redacted]	12.15	24.97	[redacted]	[redacted]

Company accepted EAG model corrections to its base case

EAG base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Undiscounted inc. QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
SOC	[redacted]	13.87	-	-	-	-	-
Fosdenopterin	[redacted]	18.97	[redacted]	5.10	10.05	[redacted]	[redacted]

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Undiscounted inc. QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
SOC	[redacted]	13.93	-	-	-	-	-
Fosdenopterin	[redacted]	18.89	[redacted]	4.96	10.43	[redacted]	[redacted]

Company scenario and EAG amendment – using seizure data

No.	Scenario (applied to company base case)	Inc. costs (£) versus SOC	Inc. QALYs versus SOC	Undiscounted inc. QALYs	ICER (£/QALY) versus SOC	Weighted ICER (£/QALY)
-	**Company base case**	[redacted]	12.38	23.07	[redacted]	[redacted]
1	**Company scenario**: use seizure frequency to estimate quality of life (simple average for seizure per day calculation)	[redacted]	7.11	13.69	[redacted]	[redacted]
2	**EAG amendment**: weighted average for seizure per day calculation	[redacted]	7.38	14.41	[redacted]	[redacted]

EAG exploratory analysis on presumptive treatment cost (deterministic)

Company: [redacted]

Bridging period – when people are suspected of having MoCD type A but before the diagnosis is confirmed by genetic test

EAG analysis including presumptive treatment cost assumption

	False presumptive diagnosis rate				
	10%	25%	50%	75%	95%
EAG base case (unweighted)	[redacted]				
7 days bridging therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28 days bridging therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unweighted exploratory ICERs

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EAG: results reflect maximum acquisition cost. Would be less if [redacted]

Fosdenopterin for treating molybdenum cofactor deficiency type A

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Cost-effectiveness results
- ✓ **Other considerations**
- ❑ Summary

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Managed access

Company has not made a managed access request

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Fosdenopterin for treating molybdenum cofactor deficiency type A

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Cost-effectiveness results
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Key issue	ICER impact	Slide
Size and nature of trial	Unknown	14
Appropriate treatment population	Large	21
Quality of life data	Unknown	23
Model's reflection of MoCD type A outcomes	Large	25
Carer burden assumption	Large	28
Cost of presumptive treatment	Small	30
Trial participants inconsistency	Unknown	51
Treatment wastage	Unknown	54

Fosdenopterin for treating molybdenum cofactor deficiency type A

Supplementary appendix

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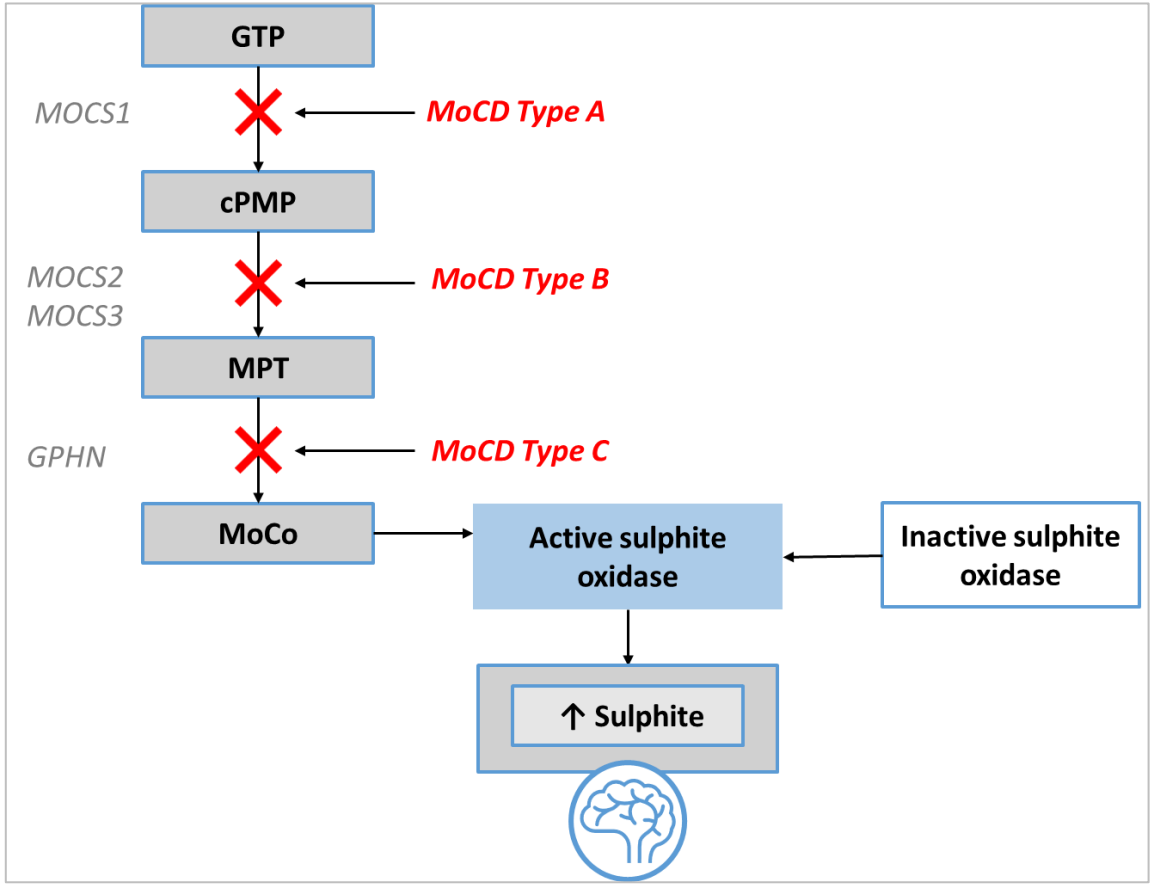
Background on MoCD type A

How MoCD type A develops



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

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People with MoCD Type A		None
Intervention	Fosdenopterin		None
Comparators	Established clinical management without fosdenopterin		None
Outcomes	Included overall survival, seizure frequency, feeding status, and HRQoL		No data presented on HRQoL in MoCD

Clinical trial results: GMFCS

EAG: interpret data with caution, untreated group more impaired at baseline than treated group (Level V, 82% vs. 44%)

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

Analysis visit result	Fosdenopterin (N=10) n (%)	SOC (N=14) n (%)
Data Availability	9	11
Level I, II, III, and IV	5 (55.6)	2 (18.2)
Level I	4 (44.4)	1 (9.1)
Level II	0	0
Level III	1 (11.1)	0
Level IV	0	1 (9.1)
Level V	4 (44.4)	9 (81.8)

Gross Motor Function Classification System (GMFCS)
Level I: generally walk without restrictions but limited in some advanced motor skills.
Level V: very little voluntary control of movement, no means of independent mobility, generally transported by their caregivers directly or in a wheelchair, and require assistance for all activities of daily living

pFAS, prospective full analysis set; GMFCS, Gross Motor Function Classification System

Clinical trial results: neuroimaging

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

	Fosdenopterin				SOC	
	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)	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

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CS, clinically significant; NCS, not clinically significant; FAS, prospective full analysis set; GMAS, genotype-matched analysis set

Clinical trial results: urinary biomarkers

Urinary biomarker results (2022 data cut)

	S-sulphocysteine (µmol/mmol)		Urinary xanthine (µmol/mmol)		Uric acid (µmol/mmol)	
	Fosdenopterin	SOC	Fosdenopterin	SOC	Fosdenopterin	SOC
Baseline	166.3	136.3	241.8	315.8	428.8	99.1
3 months	12.3	159.6	28.8	558.4	692.2	40.7
Final visit	8.6	156.6	17.9	338.2	506.4	45.0

Results normalised to creatinine

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Company treatment target reference values

- S-sulphocysteine: <50 µmol/mmol
- Xanthine: < 70 µmol/mmol
- Uric acid: >100 µmol/mmol

Clinical trial results: growth parameters

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

	Fosdenopterin	SOC	
Parameter z-score	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Weight			
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)
Height			
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)
Head circumference			
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)

NICE

cPMP, cyclic pyranopterin monophosphate; FAS, full analysis set; GMAS, genotype-matched analysis set

Company subgroup results

Early treatment (within 14 days of birth) vs late treatment (after 14 days of birth)

Most people (11/14, 78.6%) were in the early treatment group

Summary of company subgroup analysis - key outcomes

	Early treatment	Late treatment
Overall survival	No difference	
Oral feeding (n, %)	7/11 (63.6%)	0/3 (0%)
Growth pattern (median)		
head circumference	0.19	-2.52
height	-0.84	-1.40
weight	-0.26	-0.54
GMFCS (Level 1) (n, %)	4/7 (57.1%)	0/2 (0%)
Seizure (n, %)*	7/11 (63.7%)	0/3 (0%)

GMFCS, Gross Motor Function Classification System

Company:
*had seizures not present, resolved, or controlled

Key issue: Inconsistency in number of people in trials

ICER impact: Unknown

Background

- The number of people included in the clinical trial and in the economic analysis are not consistent
- Different data cuts are used for the clinical (October 2021) and economic (July 2019) analysis

Company

- No access to October 2021 individual patient level data (IPLD)
- July 2019 is the most recent data cut with IPLD with full access

EAG comments

- Unclear about company's rationale for different data cuts, IPLD required for the clinical results presented
- Inconsistency adds further uncertainty considering population size already small
- Recreating data using 2021 KM figure would add uncertainty and have minimal benefit

What is the most appropriate data cut to use for the clinical and economic analysis?

IPLD, individual patient level data; KM, Kaplan-Meier

Adverse events

Overall summary of TEAEs

	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	NA	5 (62.5)	2 (66.7)
Any SAE	8 (80.0)	7 (87.5)	2 (66.7)
Any treatment-related SAE	1 (10.0)	0	0
Any TEAE leading to death	2 (20.0)	0	0
Any TEAE leading to dose modification	0	0	0
Any TEAE leading to treatment discontinuation	0	0	0

NICE

NA, not available; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Summary of company seizure data

Seizure data submitted by the company at technical engagement

	Seizures per day	
	Fosdenopterin (n=8/11)	SOC (n=8/37)
	3.24	0.15
	4.02	0.01
	0.00	29.50
	0.00	0.08
	0.00	3.70
	2.89	0.78
	0.00	0.09
	0.01	0.30
Average	[redacted]	[redacted]

Utility values by daily seizure count from Wester et al.

Daily seizure count	Mean EQ-5D utility score*
Seizure-free	0.80
1 seizure/day	0.64
2-5 seizures/day	0.58
6 or more	0.56

*Utilities from epilepsy population

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EQ-5D, EuroQoL group-five dimension; SOC, standard of care

Key Issue: Treatment wastage

ICER impact: Unknown

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Substantial amount of treatment wasted due to vial size and storage requirement

Background

- Fosdenopterin vials (9.5 mg) need to be used within four hours, once open
- Dose is based on weight (mostly 0.9 mg/kg), any unused treatment is disposed

Company

- No current plan to introduce smaller vial size

EAG

- Wastage is substantial throughout the lifetime of a person with MoCD type A, leads to additional cost
- Wastage in first five years of a person's life amounts to about 37%
- Company's current base case includes wastage

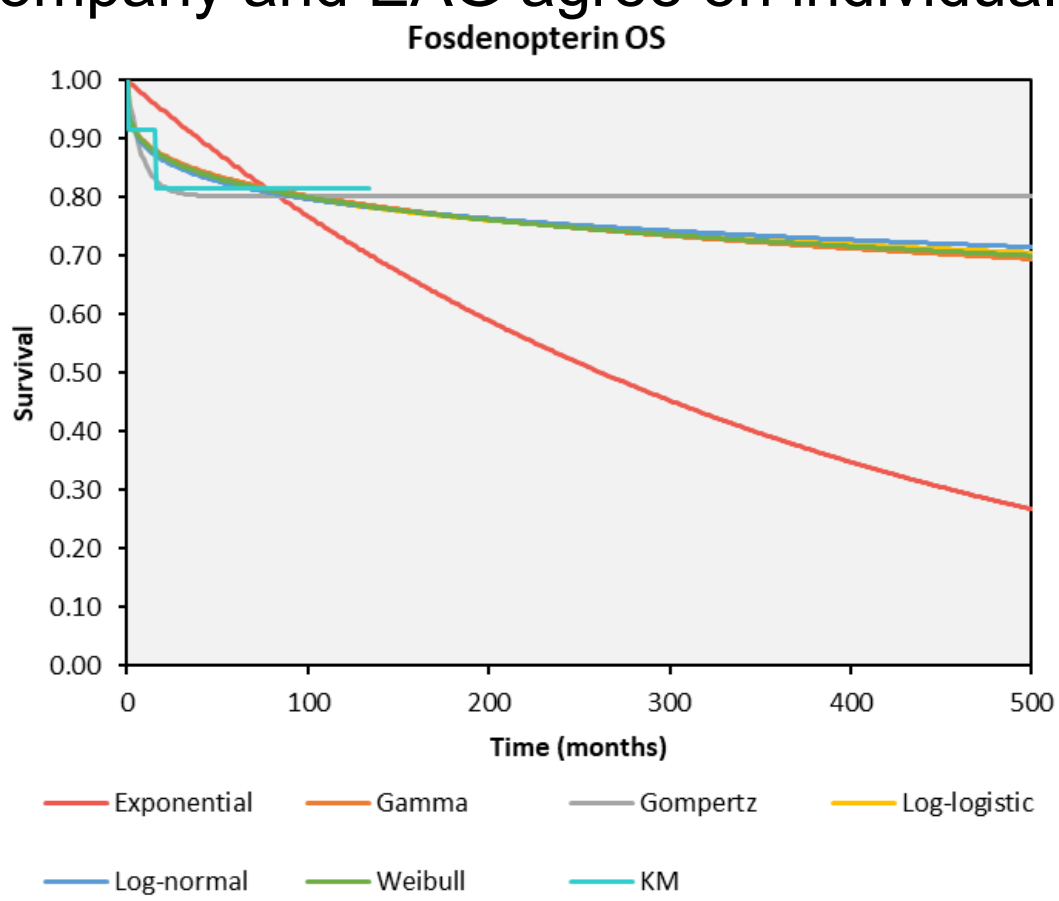
Patient organisation and clinical experts:

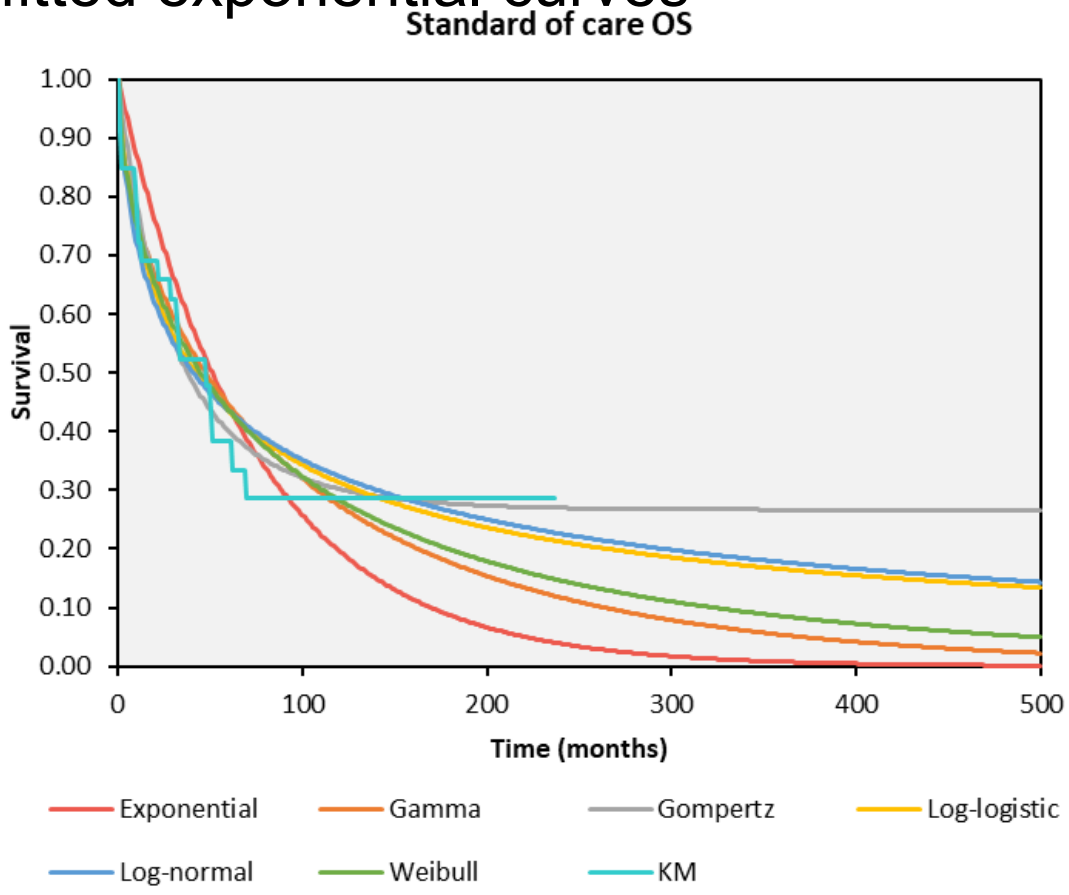
- Survey suggests wastage reduces as people get older (Metabolic Support UK)
- Most children will require a full vial after the end of the first year of life (clinical expert)

- What is the committee's view on fosdenopterin's wastage?
- Would vials be rounded up or down based on patient weight, in clinical practice?

Survival extrapolation

Company and EAG agree on individually fitted exponential curves





	Fosdenopterin	SOC
Company base case	Log-logistic	Exponential
Company base case post TE	Exponential	Exponential
EAG base case	Exponential	Exponential

EAG: true overall survival likely lies between log-logistic and exponential models

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Summary of Lund et al. study

Study type	Case report
Population	Children with non-specific developmental delays who were found to have late-onset MoCD type A
N	2
Age at diagnosis confirmation (genetic)	14 – 15 months
Intervention	Fosdenopterin
Comparator	N/A
Used in model	No

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Utility values used by company and EAG

Age	SOC		Company Fosdenopterin		EAG Fosdenopterin	
	Value	Source		Source	Value	Source
0	0.330	Lagae et al.	0.330	Lagae et al.	0.330	Lagae et al.
1	0.330		0.965	General population	0.648	A 50% improvement from the SOC arm relative to the general population
2	0.460		0.965		0.712	
3	0.460		0.965		0.712	
4	0.460		0.964		0.712	
5	0.460		0.963		0.712	
6	0.430		0.963		0.696	
7	0.430		0.962		0.696	
8	0.430		0.961		0.696	
9	0.430		0.961		0.695	
10	0.430		0.960		0.695	
11	0.430		0.959		0.694	
12	0.430		0.958		0.694	
13	0.430		0.957		0.693	
14	0.430		0.955		0.693	
15	0.430		0.954		0.692	
16	0.430		0.953		0.691	
17	0.430		0.952		0.691	
18	0.340	Lagae et al., 12-17 value with decline proportional to general population	0.950		0.645	
19	0.339		0.949		0.644	
20	0.339		0.947		0.643	
…	Continued decline		Continued decline		Continued decline	

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How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	MCD-201, -202, -501, and -502
Intervention efficacy	Overall survival: MCD-201, -202, and -501
Comparator efficacy	Overall survival: MCD-502
Utilities	Dravet syndrome utilities from Lagae et al.; completed by caregiver
Costs	BNF, eMIT; confidential PAS applied for fosdenopterin
Resource use	PSSRU, NICE TA614
Discount rate	3.5% applied to cost and QALYs
Cycle length	4 weeks
Time horizon	Lifetime (up to 100 years)

eMIT, electronic Market Information Tool; BNF, British National Formulary; PSSRU, Personal Social Services Research Unit

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EAG exploratory scenario analysis (deterministic)

Scenario description	Inc. Costs (£)	Inc. QALYs	Undiscounted Inc. QALYs	ICER (£/QALY)	Weighted ICER (£/QALY)
Company base case	[redacted]	12.38	23.07	[redacted]	[redacted]
Early-onset MoCD Type A population	[redacted]	12.88	24.28	[redacted]	[redacted]
Fosdenopterin arm utility midway between SOC and general population	[redacted]	8.48	15.12	[redacted]	[redacted]
Time to non-oral feeding to differentiate fosdenopterin group	[redacted]	5.89	10.50	[redacted]	[redacted]
People receive more than one anti-seizure medication	[redacted]	12.38	23.07	[redacted]	[redacted]
People on SOC do not visit metabolic physicians	[redacted]	12.38	23.07	[redacted]	[redacted]

EAG preferred assumptions (deterministic)

Preferred assumption	Cumulative ICER £/QALY
Company base case	[redacted]
Early-onset MoCD Type A population	[redacted]
Weight is modelled using 25th percentile data	[redacted]
People receive more than one anti-seizure medication	[redacted]
People having SOC do not visit metabolic physicians	[redacted]
People having fosdenopterin have a utility halfway between SOC and general population	[redacted]
Time to non-oral feeding to differentiate people on fosdenopterin	[redacted]
EAG preferred deterministic ICER incorporating all of the above changes	[redacted]
EAG preferred probabilistic ICER incorporating all of the above changes	[redacted]

Unweighted ICERs

Company additional deterministic scenario analysis

No.	Scenario (applied to company base case)	Inc. costs (£) versus SOC	Inc. QALYs versus SOC	Undiscounted inc. QALYs	ICER (£/QALY) versus SOC	Weighted ICER (£/QALY)
-	**Company base case**	[redacted]	12.38	23.07	[redacted]	[redacted]
1	QoL for people receiving fosdenopterin and not feeding orally have 75% improvement compared with SOC rather than similar QoL to SOC	[redacted]	9.79	19.93	[redacted]	[redacted]
2	Use seizure frequency to estimate quality of life	[redacted]	7.11	13.69	[redacted]	[redacted]

Committee decision-making framework (1/2)

Issue
Are the fosdenopterin trials suitable for decision-making?
• What is the appropriate population to apply in the model? • Does the clinical trial data sufficiently capture people with early- and late-onset MoCD type A?
Is it appropriate to apply proxy quality of life data (from Dravet syndrome)?
•Does the model capture the relevant MoCD type A outcomes? •Are people with MoCD type A expected to have general population outcomes after treatment for 1 year? •Should seizure or feeding status be used to differentiate outcomes in the model?
• Which carer burden assumption is plausible – EAG or company? • Are people with MoCD type A likely to require care beyond age 5?
Should the cost of presumptive treatment be captured in the model?
What is the committee's view on fosdenopterin's wastage?
What is the most appropriate data cut to use for the clinical and economic analysis?
What is the correct model for extrapolating survival?

Committee decision-making framework (1/2)

Issue
What is the committee's preferred ICER threshold?
What is the committee's preferred ICER?
Should a QALY weighting be applied? What is the committee's preferred weighting?
Is Chair's action appropriate for this topic?
What are the other key uncertainties?
What is the committee's view on the equalities issues raised?
Is fosdenopterin innovative?