Olipudase alfa for treating Niemann-Pick disease types AB and B [ID3913]

CON info redacted
No DPD

Highly Specialised Technology Appraisal Committee [7 November 2024]

Chair: Iolo Doull

External assessment group: Pen-TAG

Technical team: Emma McCarthy, Yelan Guo, Richard Diaz

Company: Sanofi

Olipudase alfa for treating Niemann-Pick disease types AB and B [ID3913]

- ✓ Appraisal history and appeal recap
- ❑ EAG post appeal analysis addressing upheld point
- ❑ Company addendum and EAG critique
  - ❑ Longer term efficacy and safety data
  - ❑ Qualitative data on carer quality of life in paediatric populations
- ❑ Cost effectiveness

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Appraisal history

FDG: Olipudase alfa is not recommended, within its marketing authorisation, for treating acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease) in people with type AB or type B.

DG issued	FDG issued	Appeal outcome	Actions following appeal
ACM1 October 2023	ACM2 December 2023	Appeal May 2024	Company addendum + EAG additional analyses
Not recommended – uncertainty in long term treatment effect and modelling, not cost effective	Revised company base case and additional analysis Not recommended – uncertainty in evidence and modelling, not cost effective	1 appeal point from NPUK upheld - relating **to carer QoL and disutilities**	Post-appeal analyses: Critique of additional data from company* and EAG analyses on carer disutility

ACM 3

Outline of meeting:

1. Consider appeal outcome based on additional data from company and analyses from EAG on carer disutility
2. Consider whether any changes to FDG are needed

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Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; FDG, final draft guidance; NPUK: Niemann-Pick UK; QoL, quality of life

* = No further economic analysis from company

Recap: appeal

Upheld appeal point

The Committee did not consider or fully take into account all available evidence relating to patient and carer QoL and disutilities, because it misrepresented the patient expert's position by stating in paragraph 3.17 of the FDG that *"[T]he patient expert agreed that the driver of carer requirements (and carer disutility) was the health state of the person with ASMD".*

Patient carer expert view at appeal stage

- Amount of care given not directly proportional to the severity of illness – when severity of illness is defined by increased spleen size: "……*impact of caring for a child in the lowest* [least severe] *health state was all consuming, as the child moves into the next health state, caring requirements were exacerbated by other symptoms such as neutropenia and fatigue……*"
- Model based on splenic enlargement states, but other symptoms may also affect care needs
  - Not all symptoms derived from spleen and lung function – other symptoms

Appeal panel consideration

- There are multiple drivers of carer disutility independent of the health state of the person with ASMD (emotional stress, financial loss, anticipatory grief, guilt at passing on this genetic condition)
- EAG scenario analysis demonstrated carer disutility had a significant effect on cost effectiveness
- As carer disutility was a significant driver of the cost-effectiveness of the technology, misunderstanding the significant drivers of carer disutility could potentially affect the outcome of the economic analysis.

Abbreviations: ASMD: Acid sphingomyelinase deficiency; FDG, final draft guidance; QoL, quality of life

Recap: caregiver disutility in model

Committee preferences at ACM2

- Based on patient health state irrespective of treatment
- Differential disutilities for carers to reflect bigger impact on health-related quality of life - larger disutility in more severe health state as well as in children vs adults
- Carer disutility sourced from a variety of diseases including MS and meningitis

Committee preferred disutility values and sources:

Population	Disutility, non-severe (SV < 15MN)	Severe (SV ≥ 15MN)
Paediatrics	-0.023 (meningitis and mild/moderate learning disability)	-0.080 (children with activity limitation)
Adults	-0.010 (overall utility from review of chronic diseases)	-0.045 (stage 2, symptomatic MS)

NB: carer disutility (i.e. a reduction in valued HRQoL a person experiences due to caring for a person with a condition) is often expressed as negative values, to represent negative impact of the symptom or the condition. Larger negative value = larger caregiver burden.

Abbreviations: MS, multiple sclerosis; HRQoL, health related quality of life; MN, multiples of normal SV: spleen volume

Recap: overview of committee preferred assumptions at ACM2

Assumption	Preferred assumptions	FDG section
Discount rate	1.5% discount rate for benefits and costs	3.12-3.15
Long term treatment effect	Continued treatment effect for 9 years, then frozen at year 10	3.9
Carer's disutility	As outlined in slide 5	3.17-3.18
Number of carers	1 carer	3.19
Carer disutility after bereavement	Impact considered qualitatively rather than quantitatively	3.20
Mortality	Company's parametric approach preferred to modelling mortality – with disease specific mortality for children	3.10-3.11
Weight	EAG approach to modelling patient weight, adjusted to use lower end of UK average	3.16
QALY weighting	Maximum HST QALY weighting of 2.7x applied	3.22
Uncaptured benefit	Model may have underestimated benefits associated with treatment because of how health states were defined	3.26

Abbreviations: QALY, quality adjusted life year; HST, highly specialised technologies

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EAG post appeal analysis – further exploration of carer disutility

Addressing upheld appeal point

Post appeal analyses exploring carer disutility will allow committee to:

- Understand the drivers of carer disutility independent of a person's health state (as defined by spleen volume) in the model
- Further consider accounting for treatment benefits that may not be captured by spleen volume and lung capacity (on which model health states were based)

EAG provided 3 scenario analyses:

- Removal of carer disutility from olipudase alfa arm (i.e. carers experience disutility in BSC arm only)
- Lowering of carer disutility from olipudase alfa arm (to half of the carer disutility in post ACM2 analyses)
- Sliding disutility where carer burden is reduced in early stages of disease, then increases to equal that of BSC in the most severe state (reduced by half with spleen volumes 1-6, by 25% in spleen volumes 6-15, and unchanged from ACM2 disutility value in most severe states)

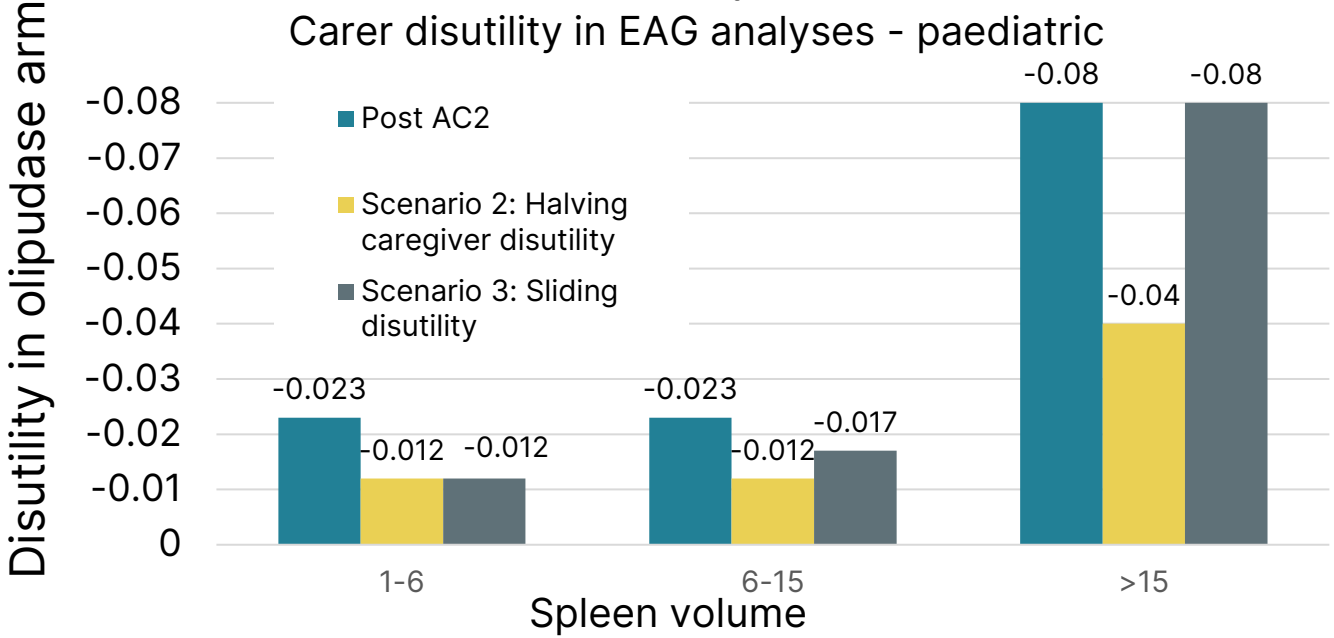
In all requested scenarios carer disutility still varies by severity as defined by spleen volumes 1-6, 6-15 and >15, with increased disutility for higher spleen volumes

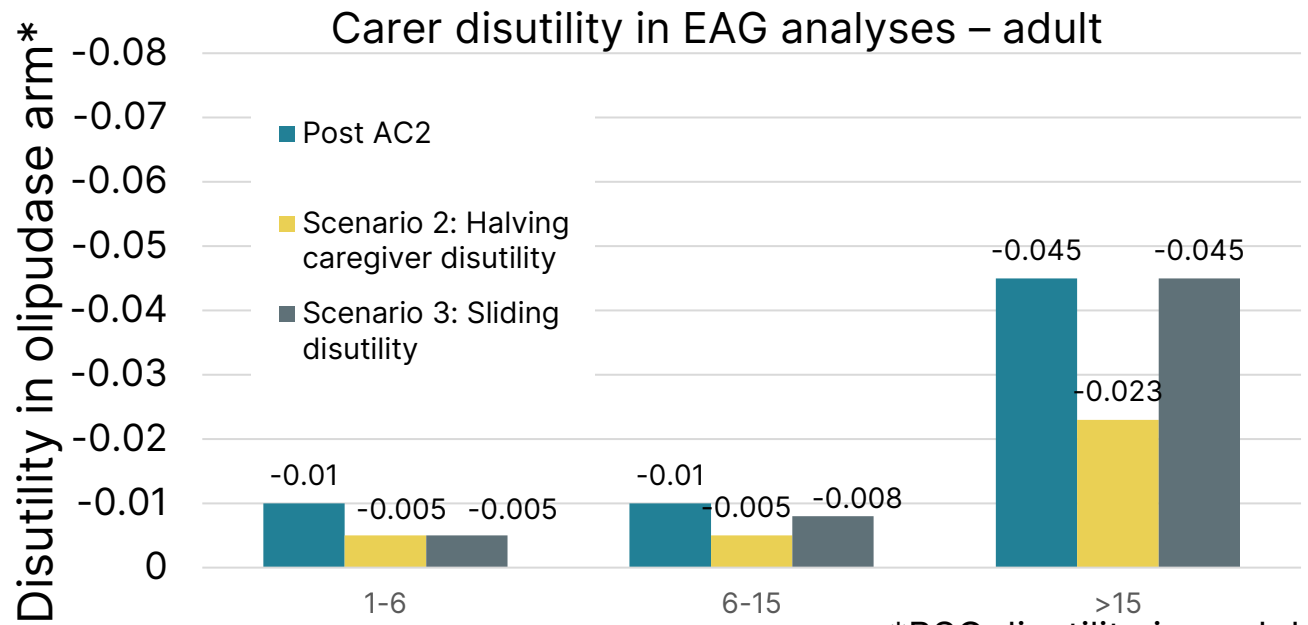
EAG consideration: degree of care needed is a function of disease progression and severity

- Committee's preferences at ACM2 reflect that significant care is required in all health states
- Removing/lowering disutility for olipudase alfa arm may account for additional benefits of the treatment in areas other than spleen volume and lung capacity

NICE technical team consideration: Uncaptured benefit may also have been partly accounted for by maximum QALY weighting of 2.7 x and 1.5% discount rate.

EAG post appeal analysis – further exploration of carer disutility





*BSC disutility in each health state equal to post AC2 values

Increased negative disutility = worse impact on carer quality of life

EAG: Zero disutility in olipudase arm (not shown) not plausible – implies people with spleen volume 1-6 need carer assistance in BSC arm only

- Contradicts appeal point

Scenario 2 and 3 plausible only if:

- difference in patients & thus caregiver QoL not already captured by model; and
- data supporting difference in carer QoL by treatment arm over and above that related to disease status/progression– no data to support this

Scenario 3: sliding disutility plausible compromise analysis if there are uncaptured benefits from olipudase alfa.

Would the committee change its preferred approach for carer disutility? If so, which scenario is preferred?

Abbreviations: BSC, best supportive care; QoL, quality of life

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Post appeal company addendum – longer term efficacy data

Data presented and committee conclusion at ACM1 and 2:

- Evidence from 4 trials considered (see slide 12): ASCEND (RCT in adults) and LTS13632, which combined participants from ASCEND-Peds (RCT in children) and DFI13412 (open-label single arm trial with adults) ongoing;
- **Committee**: improvements in clinical outcomes associated with olipudase alfa, but also noted relatively short follow up periods, high attrition and differential attrition according to different clinical outcomes in trials at 2-year follow up, and uncertainty in treatment effect of olipudase alfa in longer term

Additional evidence provided by company post appeal:

- Longer term efficacy and safety data on olipudase alfa, from:
  - ❑ Extended treatment duration period of-ASCEND [redacted] mITT population only);
  - ❑ LTS13632: all participants ([redacted]) completed, [redacted]

Abbreviations: mITT, modified intention to treat, Dlco, diffusing capacity of the lungs for carbon monoxide; HRQoL, health related quality of life

Clinical trials and studies considered at ACM1 & 2

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Clinical effectiveness mainly informed by 4 clinical trials
(1 RCT and 2 single-arm trials, all with extension studies)

Key:
- Ongoing trial
- Completed trial

Olipudase alfa (data presented at ACM1 &2)

ASCEND Peds
Open label, single arm
52 week follow up in **children** (N=**20**)

DFI13412
Open label, single arm
26 week follow up in **adults** (N=**5**)

ASCEND*
RCT + single arm extension study
2 year follow up in **adults** (N=36)

LTS13632*
Open-label extension study
4 years (**pediatric**) and 6.5-years (**adult**) follow up (N=**25**)

***Latest data cut presented at ACM3:**

- **ASCEND:** 12 Jan, 2024, median cumulative treatment duration in primary analysis period and extended treatment period [redacted] weeks for placebo arm and [redacted] weeks for olipudase alfa;
- **LTS13632:** 12 Oct, 2023, all patients(n =25) completed, no discontinuation; median cumulative treatment duration: [redacted] weeks

Clinical – percentage change in DLco (% predicted)

ACM2 FDG: The committee concluded that olipudase alfa improves clinical outcomes associated with ASMD and the treatment effect can continue into the longer term, but becomes more gradual as the person's condition moves nearer to full-health."

Predicted % DLco volume over time – ASCEND, mITT

Results - ASCEND	Placebo/OA* (N=[redacted])	OA/OA* (n=[redacted])
Mean improvement in DLco	[redacted]	[redacted]

Company - improved lung function persists in extended follow up data from ASCEND

EAG – DLco clinical outcome stable at longer follow up, consistent with previous data cuts

Would the committee change its view on olipudase alfa's treatment effect on DLco volume in the longer term?

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Abbreviations: mITT, modified intention to treat, DLco, diffusing capacity of the lungs for carbon monoxide; ASMD: Acid sphingomyelinase deficiency; ; FDG, final draft guidance; OA, olipudase alfa

*Placebo/OA = Initially received placebo, then olipudase alfa at Week 52, OA/OA = received olipudase alfa for entire duration of follow up

Clinical – percentage change in spleen volume, ASCEND

Company: continuous reduction in spleen volume in ASCEND follow up (up to week [redacted])

Spleen volume (MN) over time – ASCEND, mITT (data cut 12 January 2024)

Results - ASCEND	Placebo/OA (n=[redacted])	OA/OA (n=[redacted])
Mean % spleen volume reduction	[redacted]	[redacted]

EAG – Spleen volume reduction clinical outcome stable at longer follow up, consistent with previous data cuts

Abbreviations: mITT, modified intention to treat, ASMD: Acid sphingomyelinase deficiency ; FDG, final draft guidance; OA, olipudase alfa

*Placebo/OA = Initially received placebo, then olipudase alfa at Week 52, OA/OA = received olipudase alfa for entire duration of follow up

Clinical – percentage change in spleen volume, LTS13632

Company: Reduction in spleen volume continues in extended follow up from LTS13632

Spleen volume (MN) over time — LTS13632, safety population (data cut 12 October 2023)

Results - LTS13632	Adults ([redacted])	Paediatrics ([redacted])
Mean % spleen volume reduction	[redacted]	[redacted]

EAG – Spleen volume reduction clinical outcome stable at longer follow up, consistent with previous data cuts

Would the committee change its view on olipudase alfa's treatment effect on spleen volume in the longer term?

Abbreviations: mITT, modified intention to treat, OA, olipudase alfa; MN, multiple of normal

See appendix for data on liver volume

EAG critique of additional efficacy and safety data – overall conclusions

Efficacy:

- Data stable across key clinical outcomes (DLco, spleen volume and liver volume) across longer time periods (for between [redacted] to [redacted] years) – no evidence of treatment waning.
- Extended follow up in ASCEND shows further attrition with potential meaningful influence on results
  - Time of loss to follow up and reasons for attrition unexplained by company – ASCEND data at high risk of bias and increased uncertainty as to stability of treatment effect
- No data presented from company to show improvements in HRQoL matching clinical improvements at later time points

Safety:

- No notable increase in safety risk compared with earlier data cuts from original company submission
- High risk of TEAEs in both ASCEND and LTS13632
- EAG clinical expert – rates of adverse events may improve over time with more experience of administration of olipudase alfa at a slower rate.
- Safety data in longer term did not show meaningful tapering in risk of adverse events over time, but difficult to determine from presented data

DLco; diffusing capacity of the lungs for carbon monoxide; HRQoL; health related quality of life; TEAE, treatment emergent adverse event

Qualitative: evidence on caregivers in paediatric populations

Company:

- Evidence on the impact of rare, progressive and life-limiting paediatric conditions on informal carers' HRQoL as well as challenges associated with including HRQoL data in decision models for HTA
- [redacted]
  - [redacted]
  - [redacted]

EAG view

- [redacted]
- Quantifying and valuing caregiver burden is under-researched – but if reduction in caregiver burden is captured in benefits of the intervention, then opportunity cost of caregiver burden in other conditions should be accounted for by reducing threshold

What is the committee's view on the qualitative evidence presented by the company? Does it provide supporting information on which scenario analysis on carer's disutility more appropriate for decision making?

Abbreviations: HRQoL. Health related quality of life, ASMD: Acid sphingomyelinase deficiency

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Cost effectiveness results* post ACM2

With preferred assumptions, ICERs were substantially above £276,000 per QALY gained - Even when considering other factors such as impact of caregiver bereavement and QALY weighting, olipudase alfa was not considered cost-effective

	Incremental (olipudase alfa vs BSC)			ICER (£/QALY)
	Costs (£)	QALYs	Undiscounted QALYs	
Combined paediatric and adult population	[redacted]	16.29	27.55	[redacted]

* Deterministic base case

ICER; incremental cost effectiveness ratio; QALY, quality adjusted life year; BSC, best supportive care

Cost effectiveness results – post appeal scenario analyses addressing upheld point

In all post appeal scenarios, ICERs remain substantially above £276,000 per QALY gained

	Scenario 1 – removing carer disutility in olipudase arm		Scenario 2 - lowering carer disutility in olipudase arm		Scenario 3 – sliding carer disutility in olipudase arm	
	Inc. QALYs (discounted/ undiscounted)	ICER (£/QALY)	Inc. QALYs (discounted/ undiscounted)	ICER	Inc. QALYs (discounted/ undiscounted)	ICER
Combined paediatric and adult populations (50/50)	16.91/ 28.53	[redacted]	16.60/ 28.04	[redacted]	16.54/ 27.94	[redacted]

Should there be a change to the cost effectiveness threshold based on the additional QALY weight applied?

ICER; incremental cost effectiveness ratio; QALY, quality adjusted life year; BSC, best supportive care

Other considerations

Equality issues

- Final draft guidance prior to appeal – no equality issues identified in the evaluation

Are there any equality issues that require additional consideration?

Summary of questions for committee

EAG's scenario analyses addressing upheld appeal point:

- Would the committee change its preferred approach for carer disutility? If so, which scenario is preferred?

Additional clinical evidence provided by the company:

- Would the committee change its view on olipudase alfa's treatment effect on:
    - DLco volume and
    - Spleen volume in the longer term?

Additional qualitative evidence provided by the company:

- What is the committee's view on the qualitative evidence presented by the company? Does it provide supporting information on which scenario analysis on carer's disutility more appropriate for decision making?

Cost effectiveness and other considerations:

- Should there be a change to the cost effectiveness threshold based on the additional QALY weight applied?
- Are there any equality issues that require additional consideration?

DLco, diffusing capacity of the lungs for carbon monoxide

Factors affecting the guidance

In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

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Thank you.