Highly Specialised Technology

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Sanofi**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Niemann-Pick UK
   b. NHS England

3. **Comments on the Draft Guidance from experts:**
   a. Robin Lachmann –Clinical expert, nominated by Sanofi
   b. Simon Jones – Clinical Expert nominated by Sanofi
   c. Elaine Murphy – Clinical Expert nominated by Sanofi
   d. [redacted] – Patient expert nominated by Niemann-Pick UK
   e. James Dyson - Patient Expert, nominated by Niemann-Pick UK

4. **External Assessment Group critique of company comments on the Draft Guidancewe**
   a. Critique of company response to the DG
   b. addendum to company response to the DG

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

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID 3913]

Company response to draft guidance – Additional model results

November 2023

Version 1.0

File name	Version	Contains confidential information	Date

1. Introduction

This document contains additional model analyses as requested by the committee and confirms the company base case following the draft guidance. In addition, a scenario analysis was included for an incident patient population. The document contains the following sections:

- Base case model description
- Company base case results
- Results with assumptions based on the committee preferences
- Incident patient population scenario
- Scenario analyses based on the company revised base case and draft guidance

2. Base case model description

The company base case model is utilising the same model as in the technical engagement response. The only exception is that it has been updated by the EAG to include the potential to incorporate corrections and to run additional scenario analyses.

The revised company base case utilises the survival data submitted in company addendum, together with adjustments, made to address comments in the draft guidance. The main assumptions together with the required settings in the model are:

1) 1.5% discount rate for costs and benefits

- Implemented using the ‘Settings’ page of the model, in cells E9 and E10

2) Assumption on long-term efficacy:

- patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which all patients transition to the SV <6 / DLCO >80 state from year 10 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients’ probability to transition to the ‘SV <6 / DLCO >80’ state from the other health states between year 2 and year 10
- this change in the model is made on the ‘Clinical Inputs’ sheet, cell J4 (TP smoothing). In addition, cell E19 on the ‘Settings’ page requires to be changed to 9 years, to ensure the full effect is captured in the model

3) Overall average of 2.6 carers per patient, updated in cell F68 on the ‘Settings’ page (=0.78+0.77)

4) Assume Pompe caregiver utility decrements, updated cell H72 on the 'Utilities' page (=1)

5) For the paediatric population, set average weight of adults based on Health Survey for England 2019 data; for the adult population, set the weight of adults based on Health Survey for England 2019 data assuming the same z-score as for

18 year-olds in the existing model and assuming a standard deviation the same proportion of the mean

In addition, the company have incorporated the EAG corrections (as described in the EAG report):

- general population utility was updated based on the latest NICE algorithm
- an inappropriate correction for cycle length for the two first cycles in AE calculations;
- an inappropriate use of probabilities rather than rates in calculation of complications;
- an inappropriate correction for cycle length for the first two cycles for liver, spleen and CV complications;
- an inappropriate formula to calculate complication QALYs for all types of complications;
- dosing escalation data for children for week 6, 10, 12 and 14 were incorrectly inputted in the model.

The EAG commented on the company response to technical engagement (ID3913 Olipudase EAG TE response [ACIC], that in addition to the revised mortality approach submitted in an addendum in April 2023, the EAG noted other changes to the revised model that were not documented to the EAG and caused additional uncertainty. As discussed during the committee meeting, this was an unintentional oversight. Details of the changes made to the model between the original submission and the addendum are included in Appendix A of this document for completeness.

An additional correction was made to the model to account for the incorrect trial baseline data pulling through on the ‘Clinical Inputs’ sheet (which was from the settings for the severe sub-group model submitted in August 2022).

Additional notes on model use

The table on the ‘Settings’ sheet (G87:O94) will give the user results for adult and paediatric patients using the settings that they have chosen from the model, once the ‘Run BC analysis’ button has been clicked. That is, the user should choose their preferred model settings, then click on the ‘Run BC analysis’ button, and the table will display the results from the scenario chosen.

The user may wish to note, that in order to ensure the correct results for the paediatric population are showing on the ‘Base Case Results’ sheet, the user needs to change cell E15 to Children (<18 years), then change cell E22 to ‘One-piece fit’ on the ‘Settings’ sheet.

3. Company base case

The deterministic model results for the company revised base case are provided in Table 1.

Table 1: Company revised base case results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	22.21	[redacted]	22.05	34.87	61.09	[redacted]	[redacted]
	BSC	[redacted]	16.83	−12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	19.29	[redacted]	15.57	27.32	46.54	[redacted]	[redacted]
	BSC	[redacted]	20.89	−8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

4. Model results with committee preferences

Model results with committee preferences are provided in Table 2.

The analysis requested by the Committee has been implemented as follows:

- Analysis exploring the scenario of continuing treatment effect then freezing it at year 10. The analysis includes freezing transition probabilities at 10 years.
- Modelling mortality: the EAG's approach to modelling mortality is preferred but the company should present additional information and analysis in its revised approach for decision making. The analysis presented below was therefore based on the SMR approach with the company original assumptions relating to SMRs.
- Disease-specific mortality for children is appropriate to include in the model.
- Discount rate: 3.5% for the cost-effectiveness analysis.
- Patient weight: the EAG's approach to modelling weight is preferred but the starting weight should be at the lower end of the UK average in the model.
- Carer disutilities should be applied depending on the health state of the person with ASMD, regardless of which treatment they have.
- The EAGs approach of differential carer disutilities depending on severity of disease and whether the person with ASMD is an adult or child is preferred.
- An average of 1 carer per child with ASMD is preferred.
- There may be carer disutilities associated with patient death but this should be considered qualitatively in decision making instead of numerically in the model.

Table 2: Model results with committee preferences using the SMR approach to mortality

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	24.53	20.08	[redacted]	3.81	8.07	23.50	[redacted]	[redacted]
	BSC	[redacted]	20.73	12.01						
Adult	Olipudase alfa	[redacted]	19.11	15.00	[redacted]	4.56	5.89	11.91	[redacted]	[redacted]
	BSC	[redacted]	14.55	9.11						
Combined	Olipudase alfa	[redacted]	21.82	17.54	[redacted]	4.18	6.98	17.70	[redacted]	[redacted]
	BSC	[redacted]	17.64	10.56	–	–	–			

Abbreviations: ASMD, acid sphingomyelinase deficiency; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Since the committee requested further information on the justification for the parametric approach to mortality, results of the model using the assumptions listed above, but with the parametric approach to mortality included as opposed to the SMR approach, are provided in Table 3

Table 3: Model results with committee preferences using the parametric approach to mortality

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	24.10	19.66	[redacted]	10.80	11.66	36.85	[redacted]	[redacted]
	BSC	[redacted]	13.29	8.01	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	22.97	17.69	[redacted]	4.18	7.04	18.96	[redacted]	[redacted]
	BSC	[redacted]	18.79	10.65						
Combined	Olipudase alfa	[redacted]	23.54	18.68	[redacted]	7.49	9.35	27.91	[redacted]	[redacted]
	BSC	[redacted]	16.04	9.33	–	–	–	–	–	–

Abbreviations: ASMD, acid sphingomyelinase deficiency; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

5. Incident patient subgroup

An exploratory analysis of cost-effectiveness in an incident subgroup was undertaken following consultancy meetings with clinical experts. The patients in this subgroup may have an increased potential to benefit from treatment with olipuduase alfa compared to patients with long standing disease, as it is unlikely any permanent organ damage has taken place.

The model inputs for the incident subgroup analysis are as in the company base case with the following adjustments:

1) Starting age of patients in the model
    a. The age of patients in the model is updated from the mean age to the age at ASMD diagnosis based on the ASCEND and ASCEND-Peds trials for adults and children respectively.
        i. Mean age at ASMD diagnosis for adults: 18 years
        ii. Mean age at ASMD diagnosis for paediatric patients: 2.5 years
2) Long-term efficacy assumption
    a. patients receiving olipudase alfa can transition to an alternative health state for up to 4 years, after which all patients transition to the SV <6 / DLCO >80 state from year 5 until the end of the time horizon or death. The transition probabilities were calculated to ensure a smooth linear change in patients' probability to transition to the 'SV <6 / DLCO >80' state from the other health states between year 2 and year 5. This assumption was based on the advice received in clinician discussions.
3) Combined population
    a. In the company base case, the combined ICER is based on a 50%:50% proportion of child and adult patients. For this scenario analysis, in line with clinical advice received, we assume that the majority of patients (85%) are children

The results of the scenario analysis are presented in Table 4 below.

Table 4: Incident patient population scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	40.62	24.64	[redacted]	21.41	36.18	65.17	[redacted]	[redacted]
	BSC	[redacted]	19.21	-11.53	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	40.54	25.32	[redacted]	10.07	24.00	42.28	[redacted]	[redacted]
	BSC	[redacted]	30.47	1.32	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	40.61	24.98	[redacted]	19.71	30.09	53.72	[redacted]	[redacted]
	BSC	[redacted]	20.90	-5.11	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6. Scenario analyses

6.1 *Long-term treatment effect*

6.1.1 *Transition probabilities frozen at 10 years*

The model results for the long-term treatment effect scenario requested by the committee are provided in Table 5. The model included the assumption that patients receiving olipudase alfa can transition to an alternative health state for up to 9 years, after which patients will remain in their health state.

Table 5: Long-term treatment effect scenario results – TPs frozen at 10 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	18.25	[redacted]	22.05	30.90	54.58	[redacted]	[redacted]
	BSC	[redacted]	16.83	−12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	11.91	[redacted]	9.08	15.33	25.33	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	15.08	[redacted]	15.57	23.12	39.96	[redacted]	[redacted]
	BSC	[redacted]	20.89	−8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.1.2 *Additional long-term treatment effect scenarios*

Several additional scenarios to demonstrate the long-term treatment effect assumptions on the model are provided below.

6.1.2.1 Transition probabilities frozen after 2 years

The model results for a scenario where patients receiving olipudase alfa can transition to an alternative health state for up to 2 years, after which patients will remain in their health state are provided in Table 6.

Table 6: Long-term treatment effect scenario results – frozen after 2 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	17.29	[redacted]	22.05	29.94	52.90	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	11.98	[redacted]	9.08	15.40	25.44	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42						
Combined	Olipudase alfa	[redacted]	36.46	14.63	[redacted]	15.57	22.67	39.17	[redacted]	[redacted]
	BSC	[redacted]	20.89	-8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.1.2.2 No further transitions after 2 years (observed benefit continued)

In this scenario analysis transition probabilities were replayed in the olipudase alfa arm at two years i.e. after year two patients moved through health states based on the transition probabilities observed in year two of the trials. This was a scenario presented by the EAG in their report. The model results are provided in Table 7.

Table 7: Long-term treatment effect scenario results – no further transitions after 2 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	16.20	[redacted]	22.05	28.85	51.26	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	10.97	[redacted]	9.08	14.39	23.95	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	13.59	[redacted]	15.57	21.62	37.60	[redacted]	[redacted]
	BSC	[redacted]	20.89	-8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.1.2.3 No further transitions after 5 years (observed benefit continued)

In this scenario analysis transition probabilities were replayed in the olipudase alfa arm at five years i.e. after year two patients moved through health states based on the transition probabilities observed in year two of the trials. The model results are provided in Table 8.

Table 8: Long-term treatment effect scenario results – no further transitions after 5 years

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	17.73	[redacted]	22.05	30.38	53.70	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	11.69	[redacted]	9.08	15.11	25.00	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	14.71	[redacted]	15.57	22.75	39.35	[redacted]	[redacted]
	BSC	[redacted]	20.89	-8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.2 *Modelling mortality*

The company revised base case incorporates additional data, and a parametric approach as submitted in the Company Addendum in April 2023. Best fits were chosen for the base case based on clinical opinion. Further details have now been provided per the committee request in the company response to the draft guidance. For completeness, the tables below (Table 9 to Table 15) show results for the other curves that were not best fits for both adult and paediatric patients.

Table 9: Modelling mortality using the parametric approach – Child: Gompertz-Gompertz and Adult: Gompertz-Gompertz

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	42.52	26.82	[redacted]	12.42	28.33	50.01	[redacted]	[redacted]
	BSC	[redacted]	30.10	-1.51	–	–	–	–	[redacted]	[redacted]
Adult	Olipudase alfa	[redacted]	32.60	14.75	[redacted]	7.57	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.36	–	–	–	–	[redacted]	[redacted]
Combined	Olipudase alfa	[redacted]	37.56	20.78	[redacted]	10.00	23.22	39.05	[redacted]	[redacted]
	BSC	[redacted]	27.56	-2.43	–	–	–	–	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 10: Modelling mortality using the parametric approach – Child: Gompertz-Weibull and Adult: Gompertz-Weibull

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	43.41	27.81	[redacted]	13.34	29.35	53.35	[redacted]	[redacted]
	BSC	[redacted]	30.07	-1.54	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	38.72	22.08	[redacted]	11.21	24.56	42.67	[redacted]	[redacted]
	BSC	[redacted]	27.51	-2.48	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 11: Modelling mortality using the parametric approach – Child: Gompertz (one-piece) and Adult: Gompertz-Gompertz

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	5.41	[redacted]	11.98	21.02	28.80	[redacted]	[redacted]
	BSC	[redacted]	13.32	-15.61	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	32.60	14.75	[redacted]	7.57	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.36	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	28.95	10.08	[redacted]	9.78	19.56	28.44	[redacted]	[redacted]
	BSC	[redacted]	19.17	-9.48	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 12: Modelling mortality using the parametric approach – Child: Gompertz (one-piece) and Adult: Gompertz-Weibull

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	5.41	[redacted]	11.98	21.02	28.80	[redacted]	[redacted]
	BSC	[redacted]	13.32	-15.61	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	29.67	10.88	[redacted]	10.53	20.40	30.39	[redacted]	[redacted]
	BSC	[redacted]	19.14	-9.52	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 13: Modelling mortality using the parametric approach – Child: Weibull (one-piece) and Adult: Gompertz-Gompertz

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	22.21	[redacted]	22.05	34.87	61.09	[redacted]	[redacted]
	BSC	[redacted]	16.83	-12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	32.60	14.75	[redacted]	7.57	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.36	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	35.74	18.48	[redacted]	14.81	26.49	44.59	[redacted]	[redacted]
	BSC	[redacted]	20.93	-8.00	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 14: Modelling mortality using the parametric approach – Child: Gompertz-Gompertz and Adult: Gompertz-Weibull

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	42.52	26.82	[redacted]	12.42	28.33	50.01	[redacted]	[redacted]
	BSC	[redacted]	30.10	-1.51	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	14.75	[redacted]	9.08	18.10	28.08	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.36	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	38.28	20.78	[redacted]	10.75	23.22	39.05	[redacted]	[redacted]
	BSC	[redacted]	27.53	-2.43	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 15: Modelling mortality using the parametric approach – Child: Gompertz-Weibull and Adult: Gompertz-Gompertz

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	43.41	27.81	[redacted]	13.34	29.35	53.35	[redacted]	[redacted]
	BSC	[redacted]	30.07	-1.54	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	32.60	16.36	[redacted]	7.57	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	25.02	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	38.00	22.08	[redacted]	10.46	24.56	42.67	[redacted]	[redacted]
	BSC	[redacted]	27.55	-2.48	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 16 below shows the results using the EAG's approach to modelling mortality (that is, standard mortality ratios (SMRs) related to spleen volume) including the use of disease-specific mortality for children.

Table 16: Modelling mortality using the SMR approach scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.37	21.92	[redacted]	5.83	20.24	33.86	[redacted]	[redacted]
	BSC	[redacted]	32.53	1.68	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	25.89	6.63	[redacted]	5.36	13.21	18.52	[redacted]	[redacted]
	BSC	[redacted]	20.54	-6.57	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	32.13	14.27	[redacted]	5.59	16.72	26.19	[redacted]	[redacted]
	BSC	[redacted]	26.53	-2.45	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.3 *Discount rate*

The model results for a discount rate scenario using 3.5% for both costs and benefits are provided in Table 17.

Table 17: Discount rate of 3.5% scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	24.10	15.56	[redacted]	10.80	19.21	61.09	[redacted]	[redacted]
	BSC	[redacted]	13.29	-3.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	22.97	14.70	[redacted]	4.18	11.48	31.99	[redacted]	[redacted]
	BSC	[redacted]	18.79	3.21	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	23.54	15.13	[redacted]	7.49	15.35	46.54	[redacted]	[redacted]
	BSC	[redacted]	16.04	-0.22	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

The model results for a discount rate scenario using 0% for both costs and benefits are provided in Table 17.

Table 18: Discount rate of 0% scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	62.68	27.75	[redacted]	41.89	61.09	61.09	[redacted]	[redacted]
	BSC	[redacted]	20.79	-33.34	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	48.95	10.49	[redacted]	17.07	31.99	31.99	[redacted]	[redacted]
	BSC	[redacted]	31.88	-21.50	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	55.81	19.12	[redacted]	29.48	46.54	46.54	[redacted]	[redacted]
	BSC	[redacted]	26.34	-27.42	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.4 *Patient weight*

The model results for the patient weight scenario are provided in Table 19. The model used the assumption that weight was on the lower end of the UK average for both children and adults.

Table 19: Patient weight scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	22.21	[redacted]	22.05	34.87	61.09	[redacted]	[redacted]
	BSC	[redacted]	16.83	−12.65	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	19.29	[redacted]	15.57	27.32	46.54	[redacted]	[redacted]
	BSC	[redacted]	20.89	−8.04	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.5 *Carer disutilities*

The model results for the carer disutilities scenario are provided in Table 20. This scenario demonstrates results using the EAG preferred utility values that were applied depending on the health state of the person with ASMD, regardless of treatment. This scenario also accounts for the EAG's preference to have utility values based depend on severity of disease and whether the person with ASMD is an adult or child.

Table 20: Carer disutility scenario results – EAG preferences

		Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
	Technologies	Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	25.78	[redacted]	22.05	34.86	61.77	[redacted]	[redacted]
	BSC	[redacted]	16.83	−9.09	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	18.93	[redacted]	9.08	18.69	30.84	[redacted]	[redacted]
	BSC	[redacted]	24.95	0.24	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	22.35	[redacted]	15.57	26.78	46.30	[redacted]	[redacted]
	BSC	[redacted]	20.89	−4.42	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.6 *Number of carers (one carer per child with ASMD)*

The model results for the number of carers (one carer per child with ASMD) scenario are provided in Table 21.

Table 21: Number of carers (one carer per child with ASMD) scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	7.09	[redacted]	11.98	19.89	27.55	[redacted]	[redacted]
	BSC	[redacted]	13.32	-12.80	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	-3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	29.67	11.72	[redacted]	10.53	19.83	29.77	[redacted]	[redacted]
	BSC	[redacted]	19.14	-8.11	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

An additional scenario is provided for 1.5 carers per child with ASMD, as the patient experts stated that may be a close approximation for the number of carers (page 539 of 609 of the committee papers accessed here: https://www.nice.org.uk/guidance/gid-ta10788/documents/committee-papers). Results of this scenario are provided in Table 21.

Table 22: Number of carers (1.5 carers per child with ASMD) scenario results

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	25.31	6.55	[redacted]	11.98	20.25	27.96	[redacted]	[redacted]
	BSC	[redacted]	13.32	−13.71	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	16.36	[redacted]	9.08	19.78	31.99	[redacted]	[redacted]
	BSC	[redacted]	24.95	−3.42	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	29.67	11.45	[redacted]	10.53	20.02	29.97	[redacted]	[redacted]
	BSC	[redacted]	19.14	−8.56	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

6.7 *Carer disutilities associated with death*

The model results for the carer disutilities associated with death scenario are provided in Table 23. The model included the assumption that carer disutilities associated with death only extend for five years after death.

Table 23: Carer disutilities associated with death (bereavement) scenario results – disutilities extend for 5 years only

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	27.79	[redacted]	22.05	24.50	40.03	[redacted]	[redacted]
	BSC	[redacted]	16.83	3.29	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	24.16	[redacted]	9.08	15.57	23.46	[redacted]	[redacted]
	BSC	[redacted]	24.95	8.59	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	25.98	[redacted]	15.57	20.03	31.75	[redacted]	[redacted]
	BSC	[redacted]	20.89	5.94	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

The model results for a scenario where no carer disutilities associated with death are included in the model are provided in Table 24.

Table 24: Carer disutilities associated with death (bereavement) scenario results - no disutility associated with death

	Technologies	Total			Incremental (olipudase alfa vs BSC)				Weighted ICER (£/QALY)	Unweighted ICER (£/QALY)
		Costs (£)	LYG	QALYs (unweighted)	Costs (£)	LYG	QALYs (unweighted)	Undiscounted QALYs		
Children	Olipudase alfa	[redacted]	38.89	28.86	[redacted]	22.05	23.15	39.39	[redacted]	[redacted]
	BSC	[redacted]	16.83	5.71	–	–	–	–	–	–
Adult	Olipudase alfa	[redacted]	34.03	25.35	[redacted]	9.08	15.24	23.45	[redacted]	[redacted]
	BSC	[redacted]	24.95	10.11	–	–	–	–	–	–
Combined	Olipudase alfa	[redacted]	36.46	27.10	[redacted]	15.57	19.20	31.42	[redacted]	[redacted]
	BSC	[redacted]	20.89	7.91	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Appendix A

Five changes to the model submitted in the company addendum were made in addition to the implementation of the updated mortality approach.

Change 1

Description:	The mortality implementation for the McGovern study was slightly updated to account for it being a cumulative from baseline and not per cycle.
Sheet and cell number(s):	Model Calculations: N122:223; O122:223
Old formula:	Col N: 1-(EXP(-(EXP(-(m.childMortalityWei.param1*m.childMortalityWei.param2))*(C122^m.childMortalityWei.param2)))). Col O: 1-(EXP((EXP(-(m.childMortalityGom.param1))/m.childMortalityGom.param2)*(1 - EXP(m.childMortalityGom.param2*C122)))).
Revised formula:	Col N: (EXP(-(EXP(-(m.childMortalityWei.param1*m.childMortalityWei.param2))*(E123^m.childMortalityWei.param2))))/$N$118. Col P: selects the corrected mortality: IFERROR(MAX(J123,1-N123/N122),1) Col O: (EXP((EXP(-(m.childMortalityGom.param1))/m.childMortalityGom.param2)*(1 - EXP(m.childMortalityGom.param2*E123))))/$O$118. Col Q: selects the corrected mortality: IFERROR(MAX(J123,1-O123/O122),1)
Rationale:	Survival is cumulative from baseline and the proportional difference is now used to estimate mortality.

Change 2

Description:	Fixed a bug in the dose escalation calculation for children where only one mean dose of 0.3 mg/kg was accounted for in the schedule when there should be two (also described in the EAG response to the company response to TE).
Sheet and cell number(s):	Mean Dose Calculation: F5:O30
Old formula:	Dose #4 was originally not escalated to 0.6 mg/kg
Revised formula:	Updated to escalate dose #4 to a second step of 0.3 mg/kg
Rationale:	Corrected dosing to align with correct regimen

Change 3

Description:	Fixed a rounding error in the transition probabilities that caused a small difference in the incremental LYs between both arms when the HR was set to 1. LYs are expected to be the same when using a HR of 1.
Sheet and cell number(s):	Clinical Inputs J157, J301
Old formula:	14.2%; 2.042%
Revised formula:	14.22%; 2.041%
Rationale:	Total summation of transition probabilities were calculated to total 100%

Change 4

Description:	Updates the formula for weighted QALYs
Sheet and cell number(s):	Base Case Results: F74
Old formula:	'Model Calculations'!$HW$45*IF('Model Calculations'!$HW$45<=10,m.QALYWeight1,IF('Model Calculations'!$HW$45>=30,m.QALYWeight3,'Model Calculations'!$HW$45/10))
Revised formula:	IncQALYs*IF('Model Calculations'!HW45<=10,m.QALYWeight1,IF('Model Calculations'!HW45>=30,m.QALYWeight3,'Model Calculations'!HW45/10))
Rationale:	The actual final QALY gain is weighted according to the UNDISCOUNTED incremental results. The weight choice is based on the undiscounted incremental QALY, whereas this applies to the final Incremental QALY that is presented in the results.

Change 5

Description:	Updated the list of list of distributions on the “Lists and Constants” tab to delete un-used distributions.
Sheet and cell number(s):	Lists&Constants: D67:D73
Old formula:	Weibull; Log-normal; Generalized gamma; Log-logistic; Exponential; Gompertz
Revised formula:	Weibull; Gompertz
Rationale:	Removed unused distributions as part of model clean up.

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Olipudase alfa for treating Niemann-Pick disease types A and B [3913]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Niemann-Pick UK

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that in not recommending Olipudase alfa for the treatment acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease) type AB or type B, that the Committee has not fully understood or taken into account the high physical and psychological burden for patients (their carers and siblings) and the high level of unmet medical need that significantly impacts their quality of life. Olipudase alfa has shown significant clinical benefit and long-term impact on the quality of life and psychosocial status for patients, and their families, as detailed in evidence provided by patients and family members, who have taken time to share their lived experience, the everyday challenges they face in living with ASMD and the significant, and meaningful way in which olipudase alfa has improved their health and quality of life.
2	We are concerned that the Committee has not recognised the meaningful impact of a reduced spleen size for ASMD patients. The severity of symptoms often prevents ASMD patients from fully participating in daily activities. Spleen size in particular affects their ability to eat usual sized meals, requiring patients to eat small meals and snacks many times a day – and usually requiring the support of carers to achieve this - without ever achieving

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	necessary nutritional levels. It causes severe fatigue, affecting their energy levels and pressing on their lungs and other organs, making it hard to walk any distance, to use stairs, to attend school or work or take part in social activities. It results in bullying at school, prevents patients from buying clothes 'off the rack' and makes them feel 'different', resulting in psychological and mental health issues. An enlarged spleen also brings many clinical issues, including bruising, uncontrollable nose bleeds, slow healing, and low platelets, plus the hospital visits and interventions required to treat them, all due to this one symptom alone. Therefore, we would like to stress that a reduction in spleen size is meaningful, whether it reaches 'normal' or not, it brings significant clinical and psychological benefits, that greatly improve quality, and ability to participate, in life.
3	We are concerned about the carer disutility assumption as stated in the guidance. ASMD patients experience different symptoms and challenges, and rates of progression, with patients having variable abilities and disabilities, some requiring constant support into adulthood with significant carer burden. Therefore age / and or spleen size cannot be used to accurately predict or measure carer involvement. As symptoms are variable and severe, and dependent on disease progression, carer involvement is necessary and can be all-consuming, considering the frequent and multiple medical appointments, regular monitoring, and several different clinical teams, often located in different locations plus the challenges of coordinating appointments at any age / point of progression.
4	Whilst we agree in part with the EAG view on carer disutility associated with patient death, we are concerned that the Committee has not fully recognised the impact of bereavement on parents, carers, and siblings, who report feelings of anxiety, stress and depression, linked to their thoughts about the patient's death. Anxieties are exacerbated by constant fatigue brought by caring duties and the extreme stress in knowing the outcome of ASMD, without treatment, is death. The profound effects of bereavement and feelings of guilt, for passing on a genetic disease, or in the case of siblings, for being unaffected, can result in long-term issues, including mental health issues, that can affect ability to participate in normal life, to work, undertake social activities and to maintain family relationships for many years following bereavement. Therefore, we believe that the death of a patient has an impact for a significant period, with carer disutility reducing over time.

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5	We are concerned that the Committee has underestimated the clinical benefits of treatment and the evidence that it can overcome disease severity and reverse disease impact. Clinical data is very strong and shows clearance of storage and reversal of disease. In particular evidence shows improvements to lung function and that this improvement continues in the longer term.
6	We are concerned by the EAG's assumption that the target population for olipudase alfa would be clearly recognisable to clinicians, and we feel that the issues in accurately identifying where a patient sits on the spectrum of ASMD disease have not been fully considered. It is difficult even for leading experts, to determine the clinical distinctions of disease type A/B / disease type B early in the disease course. This results in a diagnosis of "A/B" being stated on documents and as the distinction between A/B and B often can't be determined for years, treatment should be accessible to all patients with clinically detectable disease, with clear clinical criteria for starting, and stopping treatment. Evidence supports the benefits of treating those with a confirmed A/B diagnosis, showing that treated patients experiencing increased physical and mental health benefits.
7	We are concerned about the effect of a negative decision on the patient community, who have closely followed (and participated in) the development of Olipudase Alfa since 1999. Patients and families have contributed in many ways, not just through their participation in the clinical trial. They have completed long and numerous qualitative and quantitative surveys, shared their experience by acting as a 'patient voice' at conferences and events, and given their time to support health technology assessment and regulatory processes. This small, and very well-informed patient community is well aware that Olipudase Alfa has shown significant clinical benefit, halting progression, reversing the debilitating symptoms of the disease, and extending life to the extent that the remaining health years have a significantly higher (near normal health) quality of life. They are also aware that this technology has received an interim approval in Scotland and that their peers across the border will have access under a data collection agreement, not to mention their friends in France, Germany, Brazil, Japan, and the USA. They are also aware of patients who have passed away, patients whose lives could have been saved and improved by earlier access to this treatment – and those who are awaiting a decision that will impact their future and that of their families.

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	This progressive disease has been shown to have a negative effect on the mental health of patients and families. The knowledge that there is a treatment – a treatment that works – but they can't access it, will cause significant long-term stress and anxiety for patients and their families, as well as those providing clinical care, who will not be able to provide care standards achieved in other countries.

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England

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Olipudase alfa for treating Niemann-Pick disease types A and B [3913]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	*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*. There is no access to this treatment through the NHS, some patients are receiving treatment through a Sanofi compassionate access scheme. A negative decision from NICE, would mean that no other patients could access this treatment. It is not known if Sanofi will continue to supply the drug on a compassionate basis post appraisal if the decision is negative. There is evidence that the drug is effective and that the patients who have been on the trial and who have continuing access will receive benefits that other patients will not. There is a strong clinical support for this drug as their experience has shown its effectiveness. With regard to the long term benefits of this drug, there would be some merit in pursuing a managed access agreement; the data collection would be supported by the NHS services which should improve compliance.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]

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Name of commentator person completing form:	Robin Lachmann

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that the committee has underestimated the degree of clinical response to olipudase alfa. It is striking that every parameter measured improved significantly in almost every patient treated. ASMD is a progressive disease and a successful treatment might have been expected to reduce the rate of progression or stabilise disease: olipudase alfa reverses disease. This is a remarkable result. There is complete clearance of sphingomyelin from the liver (as demonstrated by histology) and from the alveoli (as demonstrated by imaging). There is improvement of liver function (as demonstrated by lipid profiles) and lung function (as demonstrated by gas exchange). Liver and lung disease are the major causes of mortality in ASMD (the committee note that respiratory deaths are due to pneumonia, but this is secondary to the infiltration of the lung by lipid-laden macrophages and, at least in part, will have been due to lipoid pneumonia rather than infectious pneumonia).
2	I am concerned that the committee (and the disease modelling) are overly focused on the outcome of spleen volume, perhaps because it is easy to measure and the reduction in size is so striking. Spleen volumes do not normalise, but this is not surprising given the degree of splenomegaly at baseline. The histology of the spleen in ASMD is not well described, but the enlargement is not solely due to sphingomyelin or infiltration with storage cells. There is also a considerable degree of hypertrophy of the spleen and it is not

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	surprising that this persists to a degree and it is likely to explain much of the residual splenomegaly observed after 2 years treatment. In data from the phase 1b study it is striking that there is an ongoing reduction in spleen size over at least 6.5 years of treatment.
3	I am concerned that the committee has underestimated the longevity of the response to treatment. There is a remarkably rapid response in the primary outcome measures in the first 6 to 12 months of treatment, but there is also a clear ongoing improvement after that. For lung parameters it is true that, due to Covid precautions, there are fewer data available on lung function, but the data there is remarkably consistent, showing ongoing improvements in gas exchange. A manuscript describing the 2 year data from the Ascend trial is in the process of being accepted for publication and it should be possible for the sponsor to make that available to the committee. Again, in the phase 1b data, improvements in clinical parameters continue for at least 6.5 years. Once any of these parameters have normalised, it is not possible for them to improve further, but this does not mean there is not ongoing efficacy: there is no evidence that any of the beneficial effects of olipudase alfa are reversed in patients receiving long-term treatment.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Manchester University NHS Foundation trust

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Name of commentator person completing form:	Prof Simon Jones

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are very concerned that the magnitude of the response to Olipudase has been underestimated by both the company (Sanofi) and NICE. Every, measurable manifestation (and many less easily measurable) show benefit following treatment and generally continued benefit (stabilisation in the normal range or continued improvement towards normal) over the 6.5 years of published data. Experience from patients and treating investigators (including here in the UK and at our site) has been that benefit continues for over 10 years of therapy. This is different to what we see for most lysosomal treatments (and almost every other enzyme replacement therapy) in which improvement (if seen at all) is measurable for 18-24 months then there is either stabilisation or decline at a slower rate than natural history. The outcomes seen with Olipudase are vastly superior to many of the other lysosomal storage disorder treatments approved by NICE over the last 5- 10 years. The draft guidance does not reflect the significant and dramatic benefit seen by patients, clinicians or patient organisations nor our interpretation of the data.
2	We would continue to affirm that treated patients achieve a very near normal quality of life after 2-4 years of therapy. This from direct observation and assessment of treated patients
3	The clinical case for Olipudase seems very clear and straightforward to me, the only issue there can be resulting in the current draft guidance is the cost of the drug. As clinicians involved with this drug for many years I think we could agree ways to reduce the dose used as we frequently do in Gaucher disease, an analogous LSD. While this would be veering from the dose on the label we know from the long dose escalation periods that children and adults with ASMD show dramatic clinical and biomarker responses to lower doses than 3mg/kg alternate

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	weekly. A long term maintenance dose of 1mg/kg alternate weekly may be feasible for many patients and give similar results. There are adequate clinical, radiological and biochemical markers which could be used to dose titrate safely and with efficacy.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Nominated clinical expert by Sanofi. University College London Hospitals NHS Trust.

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Name of commentator person completing form:	Dr Elaine Murphy

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I believe the clinical benefit and long-term response to olipudase alfa has been underestimated by the committee. This is a treatment that works and it continues to work long-term. My personal experience of 4 adult patients receiving olipudase alfa, either through clinical trials, or post-trial access, is of continued benefit. Our adult patients have been receiving treatment for 9 years, 7 years, 6 years, and 5 years now. They show sustained benefits, with continued improvements in clinical outcomes over time, consistent with the papers of Lachmann *et al*, Orphanet J Rare Dis. 2023 Apr 25;18(1):94. doi: 10.1186/s13023-023-02700-x and Thurberg *et al*, Mol Genet Metab. 2020 Sep-Oct;131(1-2):245-252. doi: 10.1016/j.ymgme.2020.06.010. These improvements occur even in older adults with what might be considered ‘established’ disease. The treatment is well tolerated, there is no evidence of treatment ‘resistance’ developing with time and the outcomes assessed continue to move / stabilise in the correct direction (towards health).

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	I believe that appropriate treatment will significantly reduce the long-term risks of cirrhosis, disabling interstitial lung disease and cardiovascular disease.
2	Dose escalation studies of olipudase alfa in adults (Wasserstein et al, Mol Genet Metab. 2015 Sep-Oct;116(1-2):88-97. doi: 10.1016/j.ymgme.2015.05.013.0) show that even before the full (currently licensed) dose of olipudase alfa (3mg/kg alternate weeks) was reached lipid profile, plasma ceremide and chitotriosidase were falling. This, and our experience with ERT for other conditions such as Gaucher disease, suggests that once significant sphingomyelin clearance is achieved then it may be possible to maintain (some) patients on a lower dose – hence reducing costs to the NHS. This could be carefully monitored using available imaging and biomarkers.
3	Once patients are stable, then aside from their own substantial health improvements, the need for significant input and resource use across NHS services (hepatology, respiratory, gastroenterology, nutrition support, haematology, cardiology etc) will also reduce. It is not clear how this has been considered in the economic model.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] – Carer (mother) of Niemann-Pick Type B patient

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The guidance states "Best supportive care aims to manage the symptoms, such as improving nutrition and breathing, and treating infection." I am very concerned that this statement and the symptom summaries in the extended slides do not give a clear, accurate picture of the number or severity of the other symptoms and it is not made clear that "best supportive care" does very little to improve them and in consequence, the poor QoL experienced by the patient and carers. I am concerned that the following key symptoms, not related to the spleen, were omitted or not given emphasis in the extended slides and guidance. (This is relevant to the model, where other symptoms add more cost in Best Supportive Care - see details in my point 2): a. Bone thinning is mentioned in the slides. However, I would like to emphasis the bone disease which develops causes bone and joint pain and significantly reduces mobility. Sphingomyelin also builds up in the bones and patient have poor absorption of vitamin D (even with supplements). This pain cannot be treated with Ibuprofen/anti-inflammatories due to the liver involvement. Bone pain would stop my son walking even before breathlessness. He would bend down clutching his shins even as a 6yr old before the disease had progressed. Shin and arm fractures are common in NP type B children just from everyday activity. Yesterday he showed an Orthopaedic surgeon in clinic how his shins were no longer hurting following 7 months of treatment and he has asked if he can start to carry his own bag. b. In section 3.3 some best supportive care attempts are described. I would like to add that there is no best supportive care for fatigue, memory and developmental problems. I would like to give fatigue more emphasis than is mentioned in the guidance or extended slides as it has a major impact on QoL and requires a lot of 'caring'. In the slides "tiredness" has been attributed to Anaemia. It is in part; however, the fatigue is caused by a drain on energy. The cells are working

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	hard (but unable to) to remove the sphingomyelin. This state of continual draining of energy, especially when eating is prevented by nausea, results in a state of constant calorie deficiency and therefore, exhaustion. This not only effects daily activity (needing carers to help feed, move and facilitate ability to attend appointments, manage health care, and the necessities of daily life) but to attend education or work. The fact that my son was bright and motivated to study, yet so restricted by his energy levels and the resulting memory difficulties from fatigue, was a great source of mental stress for him. Treating with Olipudase Alfa has dramatically increased his energy levels, this has been life changing for him. The drain on the body's energy resources also prevents normal growth, puberty and muscle development. c. Bowel problems are not mentioned. Storage in the bowel prevents effective absorption, coupled with another symptom of daily and frequent diarrhoea, leading to a malnourished state. Food is needed frequently, at least every 2 hours (but only small amounts are tolerated due to the large liver and spleen reducing stomach capacity) and the food passing through ineffectively, means that nutritional health is very poor, as well as not consuming enough calories to support the calorific need (see my point 1b above). Treatment with Olipudase Alfa so far in 7 months has stopped the nausea (allowing my son to leave the house in the morning when well people can). He is eating bigger main meals, not needing to snack, and functioning on that chosen reduced food intake better and much longer (does not need as many calories to do more). As a carer, life no longer revolves around constant food preparation and managing his intake of food, to enable him to function. d. I would like to emphasise that Interstitial Lung Disease is a key measurable symptom which Olipudase Alfa treats and impressively reverses. To clarify, the build-up of Sphingomyelin in the lungs causes poor lung function, reducing the available area for gaseous exchange. Therefore, treatment with Olipudase Alfa is drastically improving quality of life by reducing storage in the lungs, and as a result improving lung function (reducing breathlessness and dizziness, increasing endurance). My son was breathless when walking and talking. After 7 months of treatment, he is not. Incredibly, he is playing badminton again – having had to give that up years ago when his lung function (DLCO) progressively declined to under 50%. e. Other symptoms not mentioned in the extended slides or the above list, include neutropenia, headaches, night sweats, palpitations, poor healing and skin problems. I hope I have managed to help clarify for the committee that the storage of sphingomyelin is everywhere – not simply where measured, and causes progressive deterioration on health and QoL. These are all in addition to symptoms caused by the spleen, including; abdominal pain, sleeplessness (made worse by oxygen at night), fear of rupture, low platelets (bruising, lack of clotting and healing, risk of internal bleeding) low neutrophils (frequent infection and resulting hospitalisation), and simple daily difficulties like inability to bend to put socks on, wash, wear normal clothes.

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	Storage all over the body is broken down by Olipudase Alfa effectively treating all of the disease at source, instead of fire-fighting *only a few* of the many complex symptoms, under several NHS departments. I would like to ensure the committee understand the considerable number of symptoms which it successfully treats, to fully appreciate the benefit of Olipudase Alfa. I ask the committee, does any of this information effect quality of life years?
2	In the model, I am concerned that Best Supportive Care costs have been underestimated. For example, in 'Routine Care' costs they focus only on the spleen, liver and lungs, whereas my son would also regularly see a Haematologist, Dermatologist, Gastroenterologist and Orthopaedics (Physiotherapist too, which is mentioned). His clinic appointments and tests caused 8-12 days lost per year. A greater cost is the frequent hospitalisations. As I described in my evidence, he was hospitalised for 3-14 days sometimes 4 times a year on Tazocin IV antibiotics as per febrile neutropenia protocol (neutropenic due to his Niemann-Pick type B disease). He was also hospitalised for a bleed on his liver. Therefore, for various symptoms of Niemann-Pick disease, he had over 25 emergency admissions by age 15yrs. I know of other patients who were continually hospitalised for nosebleeds and infections. This information also effects 'Indirect Costs' of 'School Days Lost' which would have been higher for my son (also affects 'workdays lost' for carers) than currently in the model. Since treatment with Olipudase Alfa his platelets and neutrophils are the highest they have ever been, therefore if treated from diagnosis at 3yrs I believe this cost and huge effect on our QoL would have been prevented. May I ask the committee to check the 'Complications' costs are realistic comparisons between Olipudase Alfa and Best Supportive Care with the clinicians.
3	Number of carers needed. I am concerned about the following assumption in the guidance, "the EAG provided different values for children and adults, arguing that children need more attention than adults, and higher values for severe disease (defined as spleen volume 15 multiples of normal or greater). The carer disutility values used by the EAG range from -0.010 to -0.080. The committee agreed that it was more logical that children and people with more severe health states would incur greater carer disutility,". In this disease it is not correct to assume that children are more unwell than adults nor that adult severity of disease can be indicated by spleen size alone. It is a progressive disease, and liver fibrosis, interstitial lung disease, fatigue, bone disease, all decline over time as storage (everywhere) increases, meaning that mobility and the ability to selfcare also decline. In addition, there are mental difficulties, isolation, dependency, depression and anxiety from coping with deteriorating health in the long term. Basing the assumption on the spleen only, is not realistic as symptoms vary person to person. Regarding carer numbers, I would like the committee to consider the amount of effort that is required on the art of the carer to allow the NHS to deliver best supportive care for both children and adults. Clinicians do not see the considerable preparation and days of recovery needed to visit hospital for clinic. To enable patient's education or work requires so much effort on the part of the carer – which is given without consideration for QoL as the carer is nearly

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	always a parent. There is no time for career, other children's care, or self. Therefore, I disagree with the committee's value of 1 carer – even on varied states of health for child or adult. In the disease community I know families with a relative less effected and in better states of heath than my son, where helping the patient battle their fatigue, malnutrition, daily limitations and mental health as well as appointments and liaison with education, work (if possible) and disability benefits is all encompassing for the families. In this disease, caring is not only providing medical practical tasks, like tube feeding. A big challenge is that the patient is cognitively aware of their decline. I agree with the company that significant care is no longer needed (and so societal benefit achieved) when the patient becomes self-sufficient on treatment.
4	I am concerned about the focus on "the Spleen remaining 6 times the size following treatment" regarding the modelling assumptions and discussion around the Near Normal Health state (criteria 2), for 2 reasons: a. When my son was under 8 years, his spleen was 12 times normal, despite some fatigue, he functioned well. As it progressed and sphingomyelin storage increased everywhere not just the spleen, he became more unwell and less able to take part in full time education or take an easy summer job. Therefore, my concern is – if when the spleen has reduced to 6 times normal after treatment with Olipudase Alfa, the patient is able to; absorb nutrition, selfcare, exercise, work, learn, fight infection, clot their blood, have the energy to be out of the house and work as a normal healthy person and be self-sufficient without supportive medical and carer care, why is that not considered a near normal health state. Why are we not measuring this on patient outcomes. If a treated patient (able to do these things) filled in a DWP PIP form they would be considered normal enough to self-care and be fully mobile so why not in this model? b. In practice this treatment would be prescribed on diagnosis – earlier than given in the trials. Therefore, the prevention of disease progression must be considered. Most children I know were diagnosed at 3yrs when the liver and spleen are first noticeably enlarged or in adults when that or other symptoms first show. At this stage the disease has not progressed so much (deterioration is slow and constant). Therefore, treating at this stage will prevent progression to the more severe health states eg liver cirrhosis. Treatment before long term progression, reverses the disease and allows the patient to have near normal health (and QoL). Clinicians frequently cite of all the enzyme replacements developed, this has been the most effective in halting and reversing symptoms.
5	I would like the committee to clarify the incidence of AB in the population with NPUK, as they appreciated in the guidance that it is lower than in the trials. The paediatric clinician explained that the effect of having B (fatigue, memory problems and slow development) can appear in young children like they could have neurological symptoms but in fact as they grow it becomes apparent by around age 7-10yrs that they have B (not got AB) and that there is no neurological involvement. It concerns me greatly that treatment guidelines could be affected by consultants (quite rightly) considering both diagnosis possibilities. The reality is that by treating A or AB on diagnosis with Olipudase Alfa, the storage in the whole body (except the brain) will be treated.

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	By successfully treating those symptoms, near normal health would be achieved for Bs and a far better state of health for ABs – so better able to cope with their neurological symptoms.
6	The statement in the guidance, "Clinical trial evidence shows that Olipudase Alfa improves lung function and reduces the size of the spleen in both adults and children with ASMD at 1 year follow up. The treatment effect may continue in the longer term, but this is uncertain" concerns me. Trials have shown significant benefit past one year but with fewer participants but surely this is understandable in a rare disease. If larger numbers are needed, can we look to the wider world patient community as long-term benefit is seen in other countries successfully treating this disease with Olipudase Alfa. In addition, the discussion around long term modelling scenarios and the phrase 'falling-off of effectiveness' also concerns me. The treatment is working just as effectively at 10yrs, but at that time the treatment is breaking down the sphingomyelin as the body is produces it. At this time, it would still be unable to break it down without Olipudase Alfa. Therefore, the treatment is effective in all ongoing years, as without it, storage would accumulate, and health would decline. In the first couple of years, it is breaking down accumulated storage so shows more dramatic results in comparative measurement. I apologise if this is stating the obvious, but I just wanted to be sure all the committee understood this, as the phrasing used in discussing the modelling sometimes sounds like the Olipudase Alfa has stopped working after so many years and this is not the case.
7	I do not agree that the recommendations are sound and a suitable basis for guidance to the NHS. Without this treatment this painful disease will progress to death or a severely debilitated QoL, whilst the burden of evermore challenging and expensive best supportive care from the NHS and carers continues. I do not feel that the patients' symptoms, severely compromised QoL, the poor QoL and demand on the carers, and just how successfully Olipudase Alfa treats this disease, has been fully appreciated by EAG, the committee's extended slides and even by the company. Treated patients are self-sufficient, contribute to society like those in normal health, and not in need of the NHS's often unsuccessful attempts at alleviating worsening symptoms. Olipudase Alfa's effectiveness is greater than clinicians, families and the company expected. Therefore, the data chosen to be collected on the trials (though clearly showing success) does not show the even greater real evidence seen by clinicians, patients and families. In this case, the clinical and patient experts are key, and I hope they have more time to contribute in the coming meeting than the first, where a new shorter format enforced time pressure on the Chair.

Insert extra rows as needed

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- Do not use abbreviations.
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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Investigator, consultant and honoraria for speaking from Sanofi
Name of commentator person completing form:	Prof Simon Jones

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are very concerned that the magnitude of the response to Olipudase has been underestimated by both the company (Sanofi) and NICE. Every, measurable manifestation (and many less easily measurable) show benefit following treatment and generally continued benefit (stabilisation in the normal range or continued improvement towards normal) over the 6.5 years of published data. Experience from patients and treating investigators (including here in the UK and at our site) has been that benefit continues for over 10 years of therapy. This is different to what we see for most lysosomal treatments (and almost every other enzyme replacement therapy) in which improvement (if seen at all) is measurable for 18-24 months then there is either stabilisation or decline at a slower rate than natural history. The outcomes seen with Olipudase are vastly superior to many of the other lysosomal storage disorder treatments approved by NICE over the last 5- 10 years. The draft guidance does not reflect the significant and dramatic benefit seen by patients, clinicians or patient organisations nor our interpretation of the data.
2	We would continue to affirm that treated patients achieve a very near normal quality of life after 2-4 years of therapy. This from direct observation and assessment of treated patients
3	The clinical case for Olipudase seems very clear and straightforward to me, the only issue there can be resulting in the current draft guidance is the cost of the drug. As clinicians involved with this drug for many years I think we could agree ways to reduce the dose used as we frequently do in Gaucher disease, an analogous LSD. While this would be veering from the dose on the label we know from the long dose escalation periods that children and adults with ASMD show dramatic clinical and biomarker responses to lower doses than 3mg/kg alternate

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	weekly. A long term maintenance dose of 1mg/kg alternate weekly may be feasible for many patients and give similar results. There are adequate clinical, radiological and biochemical markers which could be used to dose titrate safely and with efficacy.
4	
5	
6	

Insert extra rows as needed

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A Highly Specialised Technology Appraisal

EAG appraisal of the company's response to the draft NICE guidance

November 2023

Produced by

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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1. INTRODUCTION

At the first committee meeting for this appraisal, the NICE committee decided not to recommend olipudase alfa within its marketing authorisation for treating type AB or B acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease). This decision was because olipudase alfa was considered not to be an appropriate use of NHS resources at the price offered (i.e. not cost-effective) and given uncertainties in the long-term treatment effect. Following the committee meeting, NICE invited the company to submit additional evidence or rationale to address the draft guidance. Specifically, the committee requested analyses including the following:

1. Long-term treatment effect: the EAG's scenario analysis of treatment effect continuing after year 2 may be an option, but the company should present further analysis exploring the scenario of continuing treatment effect then freezing it at year 10.
2. Modelling mortality: the EAG's approach to modelling mortality is preferred but the company should present additional information and analysis in its revised approach for decision making.
3. Disease-specific mortality for children is appropriate to include in the model.
4. Discount rate: 3.5% for the cost-effectiveness analysis.
5. Patient weight: the EAG's approach to modelling weight is preferred but the starting weight should be at the lower end of the UK average in the model.
6. Carer disutilities should be applied depending on the health state of the person with ASMD, regardless of which treatment they have.
7. The EAGs approach of differential carer disutilities depending on severity of disease and whether the person with ASMD is an adult or child is preferred.
8. An average of 1 carer per child with ASMD is preferred.

(source: Draft guidance, Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease) type AB and type B, section 3.22 , NICE, 2023)

Furthermore, the committee acknowledged that carers, siblings and social networks will be affected by the death of a patient but that this should be considered qualitatively in decision making instead of numerically in the model (section 3.20, ACD).

This document contains the External Assessment Group's (EAG's) appraisal of the additional evidence submitted by the company.

2. EAG REVIEW OF COMPANY'S ACD RESPONSE

2.1. Long-term treatment effect

The company did not present new data for the long-term treatment effect of olipudase alfa, but reiterated data presented in its original submission as support. These data were based on a data cut in March 2021 and had been appraised by the EAG previously. As described by the EAG in its original report and its appraisal of the company response to technical engagement, these data are unreliable due to high levels of attrition (the data cut includes 6.5 years' of follow-up for five adult participants, and 4 years' of follow-up for spleen and liver volume in seven paediatric participants) and concerns that response to treatment may vary across patients in a way not captured by the data at these timepoints. In its original submission, the company stated that the trial was ongoing and new data would become available in July 2024.

In addition, the company conducted interviews with six clinical experts with experience of using olipudase alfa to treat people with ASMD types B and AB in the UK (three treating paediatric patients and three treating adult patients). The clinical experts treated a median of two people (range 1 to 4) with olipudase alfa. The average length of experience with olipudase alfa was not reported. The methods for the interviews, including the discussion schedule, were described in a separate document provided by the company with its submission. The schedule covered multiple topics, and the questions asked of participants were appropriate and relevant to the appraisal (the interviews were used to inform the company's response to ACD for multiple topics).

With regard to clinical experts' views on the potential long-term treatment effect of olipudase alfa, three (50%) of the experts did not feel able to make a prediction about the future waning of the treatment effect, while three (50%) experts believed that there would be no treatment waning effect. The company stated that those experts who believed there would be no treatment waning effect had longer experience with using olipudase alfa in practice, although the company did not present data to substantiate how different the groups were. One of the experts cited experience with enzyme-replacement therapy for Gaucher disease, which supports the plausibility of a long-term treatment effect for olipudase alfa. The company stated that there was agreement across experts that:

1. Paediatric patients would achieve 'normalisation' between 1.5 and 10 years, and

2. Adult patients would improve and then stabilise at 2-10 years (though those with high disease burden at the start of treatment may show reduced benefit).

The EAG assumed that these estimates were based on conjecture and that some or all experts would not have had sufficient experience with olipudase alfa to observe these effects.

The EAG noted a few limitations with the data from the interviews as reported. The methods used to analyse the contributions of participants was not described, and so the EAG was uncertain whether the company used an established method of qualitative analysis and whether any steps were taken to ensure quality control. No raw data (i.e., quotes) from the interviews were presented, results were described in narrative form only by the authors. The EAG also considered the results reported by the company to lack depth, i.e., there was a lack of detail about the discussions on each topic, attention to negative cases, variation across the sample, connections between the themes, and reflexivity on the part of the researchers. Given the breadth of the topics covered in the interview and the timeframe for the research available to the company, it may be that full qualitative analysis of the interview transcripts was not feasible for the company, though this does increase the uncertainty in the findings. In particular, with regard to the discussions on long-term treatment effect, the EAG was uncertain to what extent the conclusions of experts were based on direct experience as opposed to beliefs based on the data available to date, how much difference in length of experience there was between the two perspectives on treatment effect waning, to what extent the included clinicians had treated people with ASMD that had dropped out of the trials early, what factors influenced the broad estimated response range for patients (described as between 1.5 and 10 years for children and 2-10 years for adults), and how 'normalisation' was defined by participants. Fundamentally, the EAG considered that the evidence from the interviews was useful to the appraisal, but that the lack of detail in the results and the uncertainty about the methods used to analyse participants' submissions limited its influence in resolving uncertainties raised by the committee in its draft guidance.

Overall, the EAG's position remains the same as described in its previous report, which is that it is plausible that olipudase alfa may have a long-term treatment effect, however there were no data to substantiate this. Given the risks of overestimating the incremental QALY gain associated with olipudase alfa, and evidence that treatment response may vary across the population, there was a great deal of uncertainty surrounding long-term efficacy assumptions.

2.2. Modelling mortality

The company altered their approach to modelling mortality in an addendum appraised by the EAG during technical engagement. This change in approach was to incorporate international chart review data (N=270). In its response to ACD, the company did not provide further data on mortality risk but provided some additional files to justify its approach to modelling mortality in its evaluation to address the committee's uncertainty about the approach chosen, specifically exploring the standard set of survival functions, piece-wise fitting and use of splines. The company provided a description of the fit indices used to select optimum survival curves.

Overall, the EAG's concerns as to the provenance of the data remain, in particular the observation that only 10 of 42 paediatric deaths (23.8%) were known attributable to ASMD, with the majority (31, 73.8%) classified as unknown. The EAG notes that overall childhood mortality (to age 5) is lower in the UK compared with all countries in the study except Germany, which provided only 33/270 (12%) of observations (mortality rates: UK 4.2 vs Brazil 14.7, USA 6.3, France 4.4, Germany 3.7 per 1000 live births, World Bank, 2020).

Mortality amongst the adult cohort was low with 6 deaths overall. However, 2 were classed as related to ASMD with 4 (66%) classified as unknown.

On balance, given the uncertainties and lack of reporting of causes of mortality, the EAG prefers to retain mortality estimates based on disease status as originally provided by the company based on spleen volume (which is consistent with committee preferences).

2.3. Disease-specific mortality in children

The company did not present any additional evidence on this topic.

2.4. Discount rate

The NICE committee concluded that a discount rate of 3.5% should be used in the economic analyses, as is consistent with the NICE reference case. The company had previously argued that this appraisal met the NICE criteria for a reduced discount rate of 1.5%, which improves the cost effectiveness of health technologies (particularly those with high upfront costs and delayed benefits). However, the EAG and the NICE committee did not think there was sufficient evidence to conclude that olipudase alfa met criteria 2 and 3 (that treatment is likely to restore people with ASMD types B and AB to full or near-full health and the benefits are likely to be

sustained over a very long period). The company sought to provide further support for these two criteria, which is appraised in the following sub-sections.

2.4.1. Criterion 1 'people with ASMD would otherwise die or have very severely impaired quality of life'

The committee considered that ASMD likely severely impairs quality of life but the mortality risk was unclear. As discussed in Section 2.2, mortality estimates for this appraisal remain highly uncertain. As such, the EAG agreed with the committee that the mortality risk of ASMD is uncertain.

2.4.2. Criterion 2 ' the treatment is likely to restore people to full or near-full health'

The company submitted data from interviews with clinicians (methods critiqued by the EAG in Section 2.1) that over several years some people with ASMD treated with olipudase alfa would return to normal or near normal health. Those who it was considered may not experience this benefit included people with neurological symptoms, which are not expected to improve with treatment, and those who develop irreversible organ damage before the start of treatment. There were no clear estimates for the proportion of people with ASMD who met these criteria in the prevalent population, and the company acknowledged limitations with the best estimates they were able to provide. If olipudase alfa was available and people with ASMD received treatment early following diagnosis, the EAG agreed with the company that it was plausible that the proportion of people with irreversible organ damage would be reduced, though noted that there was no long-term evidence to determine the actual number of people who develop organ damage following initiation of olipudase alfa. Approximately 10% of the adult population with ASMD exhibit neurological symptoms, which may be a reasonable estimate of this population given that some of the neurological symptoms identified in childhood may represent other issues unrelated to ASMD that may resolve before adulthood.

The EAG assumed that the views of clinicians were based on their beliefs about what is plausible based on the available data. At present, based on the evidence available and as discussed in previous reports of the EAG appraisal, there was no clear evidence that olipudase alfa results in a return to full or near full health in those treated. At the final follow-up of evidence available (for which there is a high amount of missing data), people treated exhibited spleen volume, liver volume and respiratory function meaningfully below the norm. While these effects would nevertheless be of meaningful benefit to those people who experienced them, the EAG

did not consider there to be evidence to confirm that these benefits would be consistent with near normal or normal health. Moreover, as there was variation in response across the sample, the EAG did not consider that there were data to conclude that a near or normal health outcome was likely for those treated.

Finally, the company stated that people with ASMD are 'often lighter and shorter than the general population' (p13, company response) and that 'patient height… can have a large impact on psychological wellbeing' (p18, company response). The company assumed a below-normal weight for adults (to calculate drug dosing and hence cost), further supporting deviation from normal or near-normal health status.

Following the company's response to the ACD, the EAG maintained its view that olipudase alfa did not meet this criterion for a non-reference case discount rate.

2.4.3. Criterion 3 'the benefits are likely to be sustained over a very long period'

As stated in Section 2.1, the EAG still considered there to be uncertainty about the long-term effect of olipudase alfa, meaning that it did not consider there to be evidence that the benefits of olipudase alfa were likely to be sustained over a very long period of time. The EAG therefore considered that olipudase alfa did not meet this criterion for non-reference case discounting.

2.5. Patient weight

The company adopted the committee's approach to modelling patient weight in the economic analysis. However, the EAG identified an error in the company's calculation of standard deviations which it has corrected.

2.6. Caregiver utilities

The committee requested that 'carer disutilities should be applied depending on the health state of the person with ASMD, regardless of which treatment they have' and that 'the EAG's approach of differential carer disutilities depending on severity of disease and whether the person with ASMD is an adult or child is preferred'.

The company adapted its approach to apply caregiver utilities according to patient health state, as preferred by the committee. However, the company assumed the same care-giver disutilities for adults and children and retained its use of disutility values from a Pompe disease population. No further evidence was used to substantiate this position, and the EAG maintained its view on

the basis of clinical expert opinion that Pompe disease was not an appropriate proxy condition for this appraisal. The EAG retained its preference for a more conservative approach using proxy values from other conditions including MS and meningitis.

2.7. Number of caregivers

The committee expressed a preference for one caregiver per child and adult. The company agreed that one carer was appropriate in adults but preferred to assume 2.6 carers for children. The company did not provide additional evidence to support its position. As described by the EAG in its previous reports for this appraisal, the EAG considered this issue to be less about the impact of ASMD on carers and more about the methodological approach used to consider carer disutility within a HTA submission to NICE.

The EAG reiterates its position that whilst it acknowledges that the disease has an impact on carers, the purpose of the appraisal committee is to allocate finite resources fairly and equitably. Existing willingness to pay thresholds used by the NICE committees were conceived as the QALYs accrued to a single patient, without consideration of the benefits to carers. When an appraisal includes the benefits accrued to more than one individual, the threshold should theoretically be lowered accordingly to ensure a level playing field. A reasonable reduction could be proportionate to the number of individuals whose health gain is included. The HST programme has a stronger remit to consider the impact on carers than in the TA process, therefore the EAG feels that an acceptable compromise is to consider a single carer, whilst bearing in mind the implications of this on the cost-effectiveness threshold.

2.8. Impact of bereavement

The committee preferred for the impact of bereavement on carers (and by extension, siblings and social networks) to be considered qualitatively rather than numerically within the decision model. The company retained its position that the death of a patient results in a permanent decrease in utility of -0.5 for the remainder of the model time horizon (100 years), though explored a shorter time period for the utility decrease in a scenario analysis. The EAG noted that the company's preferred approach did not consider the remaining life expectancy of the carer, and maintained its position that this is an overestimate in both impact and duration. While some authors have considered the potential for including utility decreases related to mortality in economic evaluations, there are a number of methodological uncertainties outstanding that mean that this is not accepted practice. This is also not an established approach in the NICE

reference case, which means that its inclusion in this model would undermine consistency and fairness of the NICE process. The EAG therefore has not changed its base case.

2.9. Trial generalisability

The NICE committee noted various factors that may be heterogeneous across the ASMD population and while they considered that the populations in trials may be representative of those seen in the NHS, there were uncertainties about whether the trials included the range of people who would have olipudase alfa in clinical practice. This was largely due to uncertainties in the proportion of participants in the trials with ASMD type AB (this was not recorded in the trial), the typical height and weight of people with ASMD, and the exclusion of people with the most severe and mild disease from the trials. The company included discussion of this issue in its interviews with clinical experts (methods for which are critiqued in Section 2.1). The company reported that experts considered it plausible that those with mild and severe disease not included in the trials could have a comparable response to those included. As noted in the EAG report for this appraisal, subgroup analysis conducted by the company did not show variation in treatment effect according to baseline severity, though these analyses were limited due to small sample size. Overall, the EAG considered there to be no evidence that the treatment effect would vary according to baseline severity, but that further evidence was needed to rule out this possibility. No other evidence was submitted by the company.

2.10. The impact of olipudase alfa on patients' quality of life

The committee highlighted the absence of a clear effect of olipudase alfa on patients' quality of life in adults and limitations in quality-of-life data with children. The company did not present new data but discussed some of the findings from exit interviews with trial participants. The methods used to elicit these data were not presented, nor was a full discussion of the data from the interviews. The company stated that some participants discussed how they only appreciated the impact of their condition on their quality-of-life following treatment, and that they experienced improvements in self-worth, self-confidence, worry, fatigue, and functioning. As stated in the EAG report, the EAG considered that the clinical benefits reported following olipudase alfa would likely improve quality of life, though the magnitude of this benefit was uncertain. Measures used by the company to assess fatigue, pain and functioning did not capture any differences between participants receiving and not receiving olipudase alfa. While the EAG maintained its view that those people who benefit clinically from olipudase alfa would also

experience improvements in their quality of life, the magnitude of this benefit in those individuals and across the population was uncertain. This adds uncertainty to cost effectiveness estimates.

2.11. Clinical impacts of olipudase alfa not captured in the economic model

The company suggested in their response that some aspects of ASMD and benefits of olipudase alfa were not captured in their economic model and so have not been factored into cost effectiveness estimates. The company provided a list of possible factors based on discussions with clinical experts. The EAG disputed that some of these were not captured in the company's model, as several of these factors were incorporated into the vignettes used by the company to inform health state utilities. For example, vignettes described the impact of the condition on fatigue, ability to function, abdominal pain and discomfort, exercise tolerance, emotional impacts, hospitalisation, infections, minor bleeding events, ability to eat normally, reduced height, muscle strength and school attendance. Of the factors suggested to the company by its clinical experts, the EAG considered that only severe bleeding complications, splenic crises, and high cholesterol levels necessitating treatment were not captured in the vignettes (though the model included complication costs of bleeding (as a result of increased spleen volume), liver, spleen and cardiovascular complications).

The EAG also disputed the company's claim that "all of these symptoms are improved and mostly brought within normal range with olipudase alfa". The company evaluated change on measures of fatigue, pain, and functioning in their pivotal trial, none of which showed a benefit of olipudase alfa after one year of treatment. As noted in the EAG report, while numerical benefits of olipudase alfa were seen for exercise tolerance and cholesterol levels, the company did not report validated thresholds to determine whether these differences were of clinical significance.

Overall, the EAG did not consider there to be clear evidence that key factors that may influence the cost effectiveness of olipudase alfa were not captured in the economic analysis.

2.12. Model changes

The company made a series of changes to their model in their response. These are described in Section 3.

2.13. Factual inaccuracies

The EAG thanks the company for highlighting the error in cell Clinical Inputs!H251, but noted that the version of the model supplied to the EAG retained this error. As part of its revised base case the EAG removed the relevant scenario (as it was rejected by the committee) thus the error is no longer of consequence to the analysis.

3. EAG APPRAISAL OF THE COMPANY'S REVISED ECONOMIC MODEL

3.1. Long-term treatment effect

The company's original submission drew on data from the ASCEND trial for the first 12 months before assuming all patients move to the best health state at two years. At technical engagement the company modified this, freezing transition probabilities from years 2-9, followed by moving all patients to the best health state at year 10. This implied that 2.26% of patients would be in the best health state at one year, 7.67% at two followed by gradual improvement (at a declining marginal rate forming a concave curve), before jumping to 98.91% at year 10 (with 1.09% mortality). The EAG felt this was not a plausible extrapolation of the observed data (Figure 1).

Following AC1, the committee requested a scenario "of continuing treatment effect then freezing it at year 10" (ACD, section 3.22). The EAG believes that the company's approach is an incorrect interpretation of the committee's preferred scenario: the company's revised model implements a smoothed acceleration in treatment effect from year 2 to 10, with assumption of perfect effect from year 10 onwards, before freezing the transitions with all patients in the best health state (Figure 1). The EAG noted that this represents an even more optimistic scenario than the company's previous assumptions with a higher proportion of the cohort responding earlier.

The EAG has therefore implemented a scenario that continues the treatment effect by maintaining constant transition probabilities from year 2 onwards and freezes all further transitions from year 10 (except for mortality, Figure 1). This matches the company's AC1 base case, but without the jump to perfect health at year 10. The EAG noted that this scenario implied a continued increase in effect at a declining rate from year 2 to around year 5 or 6, by which time the proportion in the best health state stabilises (with a slight decline due to mortality effect). This is driven by continued improvement in spleen volume, but very little improvement in DLCO (according to the transition probabilities derived from the data, a patient has only around a 50% probability of remaining in the best DLCO state each year, Figure 2 and Figure 3).

Figure 1: Proportion of cohort in best health state by time (adults)

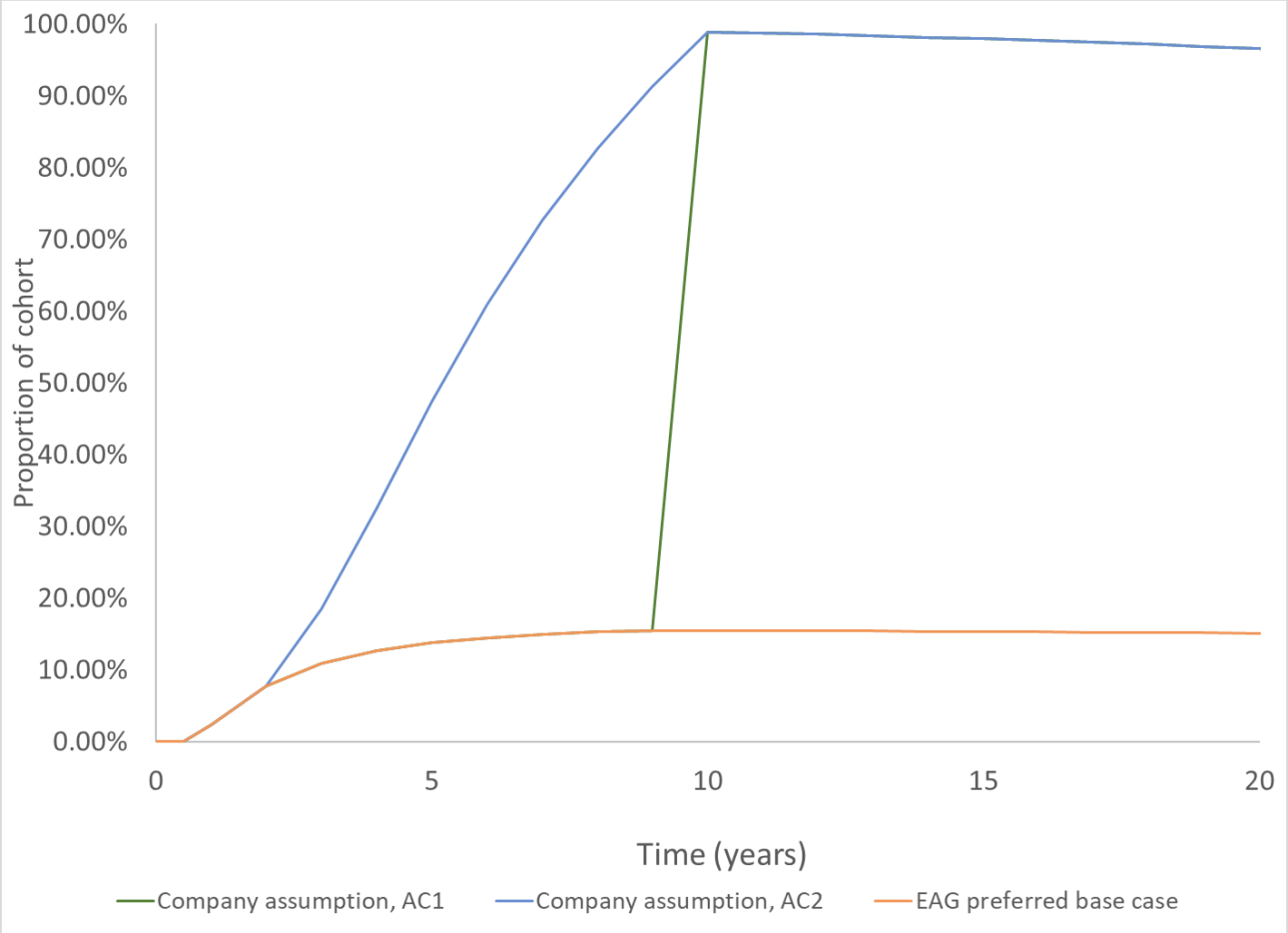

Figure 1 shows the Markov trace for the proportion of the cohort in the best health state (DLCO>=80, SV<6) at each time point illustrating the company's pre- and post-AC1 assumptions and the EAG's preferred base case. The observed data inform the functions as far as year 2, with subsequent portions of the lines representing the company and EAG's extrapolations. The EAG feels the company's assumptions are not reasonable extrapolations of the observed data.

Figure 2: Proportion of cohort in best SV state (SV<6, adults)

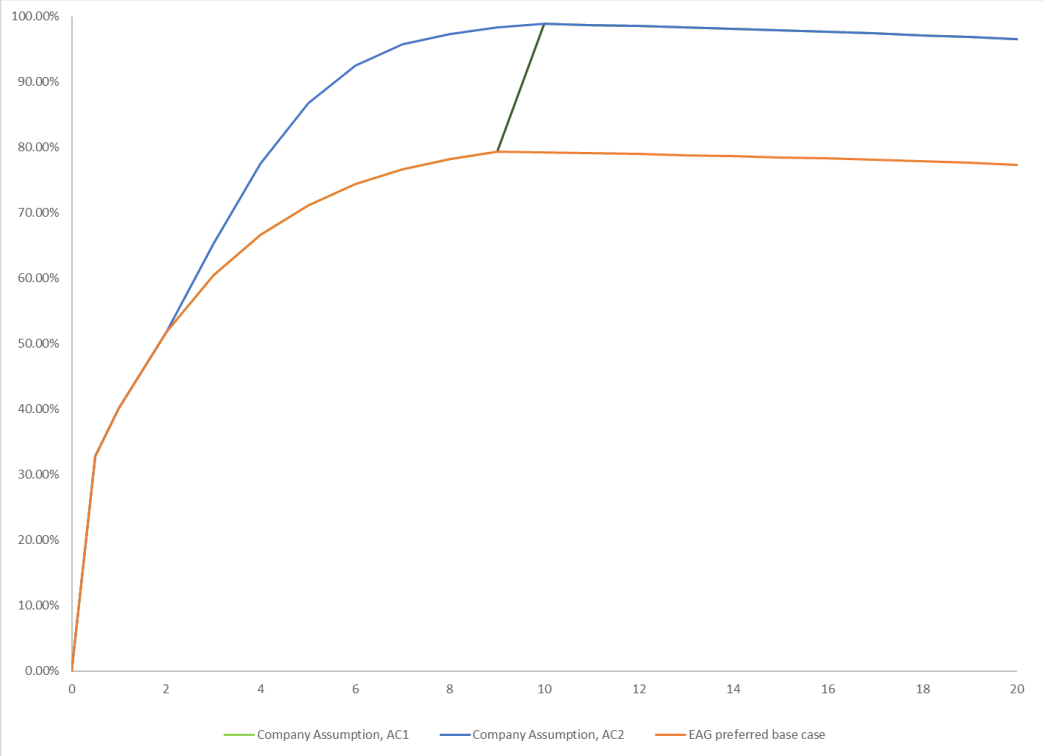

Figure 2 shows the Markov trace for the proportion of the cohort in the three best spleen volume states (SV<6) at each time point illustrating the company's pre- and post-AC1 assumptions and the EAG's preferred base case. The observed data inform the functions as far as year 2, with subsequent portions of the lines representing the company and EAG's extrapolations. The EAG feels the company's assumptions are not reasonable extrapolations of the observed data.

Figure 3: Proportion of cohort in best DLCO state (DLCO>=80, adults)

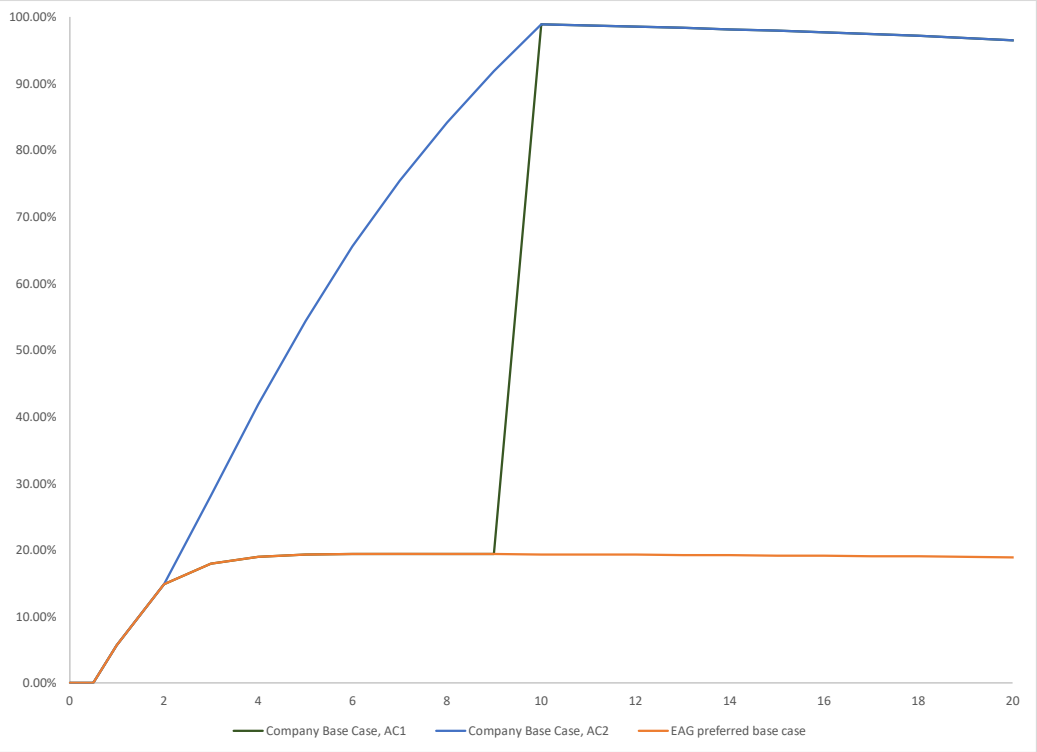

Figure 3Figure 2 shows the Markov trace for the proportion of the cohort in the three best lung health states (DL_{CO}>=80) at each time point illustrating the company's pre- and post-AC1 assumptions and the EAG's preferred base case. The observed data inform the functions as far as year 2, with subsequent portions of the lines representing the company and EAG's extrapolations. The EAG feels the company's assumptions are not reasonable extrapolations of the observed data.

3.2. Patient weight

The EAG believed that the company had made an error in its approach to modelling the weight of children with ASMD which was used in its scenario incorporating the committee's preferences (the company used the EAG AC1 base case for patient weight in its own base case). In its revised model, the company subtracted the standard error of weight from the mean for each age, then further modified this for the z-score. The EAG therefore modified the approach, retaining the Health Survey for England 2019 data means, and calculating standard deviations from the reported standard errors and (unweighted) bases, which were then modified by the company reported z-scores within the model. The impact of this was to reduce the expected weight of patients with ASMD.

4. EAG REVISED BASE CASE

There remain several continuing differences between the committee's preferred assumptions and those preferred by the company (Table 1). The EAG made no corrections to the company base case (but corrected the approach to calculating patient weight in the relevant scenarios).

The EAG was unsure whether the interpretation of the committee's preferred treatment effect was erroneous or that the company proposed the acceleration in effect as its main scenario. The EAG has therefore not included this in its corrected company base case, but as a comparative scenario with the EAG's preference.

The EAG has adopted the committee's preferred assumptions. Therefore, the EAG base case remains the same as per AC1 except for:

- Observed benefit / treatment effect
    - Previously the EAG froze transitions at 2 years. As per committee preference, treatment effect continues for 10 years, after which transitions are frozen
- Paediatric mortality
    - The EAG base case now includes paediatric mortality
- Patient weight
    - The EAG base case is based on HSE 2019 data, adjusted for z-scores of people with ASMD, representing a below normal weight.

Table 1 Comparison of Committee, Company and EAG preferred base case

Assumption	Committee preferred base case	Company preferred base case	EAG response	Agreement
Long-term treatment effect	"The EAG's scenario analysis of treatment effect continuing after year 2 may be an option, but the company should present further analysis exploring the scenario of continuing treatment effect then freezing it at year 10"	Increase in treatment effect from year 2 to 100% by year 10, then freezing transitions from year 10 onwards.	Continuation of treatment effect from year 2 to year 9 (i.e. transition probabilities remain constant), with transitions frozen from year 10 onwards.	✗

Assumption	Committee preferred base case	Company preferred base case	EAG response	Agreement
Mortality	"The EAG's approach to modelling mortality is preferred but the company should present additional information and analysis in its revised approach for decision making"	BSC survival based on chart review, olipudase survival based on general population mortality adjusted by HR.	As per committee preference (SMR based on splenomegaly)	✗
Disease specific mortality for children	Include	Include	Include	✓
Discount rate	3.5%	1.5%	3.5%	✗
Patient weight	"Patient weight: the EAG's approach to modelling weight is preferred but the starting weight should be at the lower end of the UK average in the model"	As per EAG AC1 (mean weight from HSE 2019)	As per committee preference	✗
Carer disutilities (1)	Carer disutilities should be applied depending on the health state of the person with ASMD, regardless of which treatment they have.	As per committee preference	As per committee preference	✓
Carer disutilities (2)	The EAGs approach of differential carer disutilities depending on severity of disease and whether the person with ASMD is an adult or child is preferred.	Same carer disutilities for adults and children	As per committee preference	✗
Carer disutility values	-	Equal in severity to Pompe disease	Analogues to similar severity conditions	✗

Assumption	Committee preferred base case	Company preferred base case	EAG response	Agreement
Number of carers (child)	An average of 1 carer per child with ASMD is preferred.	2.55	1	✗
Number of carers (adult)	-	1	1	✓
Carer disutility from patient mortality	Exclude from model and consider qualitatively	-0.5 in perpetuity (end of model run, 100 years)	Exclude from model and consider qualitatively.	✗

Table 2: EAG's deterministic preferred assumptions and ICER (unweighted, paediatric population)

	Incremental cost	Incremental QALYs	ICER (applied individually)
Company's base case	[redacted]	34.87	[redacted]
EAG / committee preferred base case assumptions (applied individually)			
Costs and benefits discounted at 3.5%	[redacted]	19.21	[redacted]
Mortality based on splenomegaly	[redacted]	22.44	[redacted]
Removed carer disutility associated with death of patient	[redacted]	23.15	[redacted]
Treatment effect continues to year 10, further transitions frozen.	[redacted]	30.41	[redacted]
Patient weight: lower end of HSE2019 data	[redacted]	34.87	[redacted]
Alternative approach to modelling carer disutility			
Magnitude of carer disutility	[redacted]	34.86	[redacted]
1 carer for children	[redacted]	33.69	[redacted]
Cumulative impact of EAG's preferences	[redacted]	7.90	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 3: EAG's deterministic preferred assumptions and ICER (unweighted, adult population)

	Incremental cost	Incremental QALYs	ICER (applied individually)
Company's base case	[redacted]	19.78	[redacted]
EAG / committee preferred base case assumptions (applied individually)			
Costs and benefits discounted at 3.5%	[redacted]	11.48	[redacted]
Mortality based on splenomegaly	[redacted]	14.73	[redacted]
Removed carer disutility associated with death of patient	[redacted]	15.24	[redacted]
Treatment effect continues to year 10, further transitions frozen.	[redacted]	15.13	[redacted]
Patient weight: lower end of HSE2019 data	[redacted]	19.78	[redacted]
Alternative approach to modelling carer disutility			
Magnitude of carer disutility	[redacted]	18.69	[redacted]
1 carer for children*	[redacted]	19.78	[redacted]
Cumulative impact of EAG's preferences	[redacted]	5.81	[redacted]

*Only applies to children so no change from base case for adults. Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

4.1. QALY weighting

The undiscounted incremental QALYs accrued to the patient (excluding caregivers) for the paediatric and adult cohorts according to the EAG base case are shown in Table 4. The multiplier can be either applied to the incremental QALYs, resulting in an adjusted ICER which should be compared to the typical £100,000 threshold, or by adjusting the threshold itself, against which the unadjusted ICER should be compared. For context, the opportunity cost of applying the weighting is shown in terms of the expected lives foregone elsewhere in the NHS, assuming the NHS generates a QALY for every £20,000 to £30,000 expenditure.

Table 4 QALY weighting

Population	Undiscounted Incremental QALYs	Multiplier	Adjusted ICER	Adjusted threshold	Opportunity cost vs STA threshold*
Paediatric	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Opportunity cost in terms of lives foregone elsewhere in the NHS to save the equivalent of one life with olipudase alfa, calculated at £20,000 / QALY and £30,000 / QALY

Olipudase alfa for treating acid sphingomyelinase deficiency (Niemann-Pick disease type B and AB) [ID3913]

A Highly Specialised Technology Appraisal

EAG appraisal of the company's response to the draft NICE guidance: Addendum with additional table

November 2023

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1. INTRODUCTION

Table 4 of the EAG ACD response illustrated the effect of the QALY weighting multiplier on the ICER, based on incremental QALYs accrued to the patient alone. Table 4a below provides an alternative version of the table including incremental QALYs accrued to both patient and carers.

Tabel 4a QALY weighting

Population	Undiscounted Incremental QALYs	Multiplier	Adjusted ICER	Adjusted threshold	Opportunity cost vs STA threshold*
Paediatric	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adult	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Opportunity cost in terms of lives foregone elsewhere in the NHS to save the equivalent of one life with olipudase alfa, calculated at £20,000 / QALY and £30,000 / QALY