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)

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness *Would it be appropriate to refer this topic to NICE for evaluation?*	Sanofi	Yes	Thank you for your comment.
	Niemann-Pick UK (NPUK)	We support the referral of this topic to NICE for evaluation.	Thank you for your comment.
	NHS England and Improvement	Yes it is appropriate	Thank you for your comment.
Wording	Sanofi	The following wording would more closely reflect the proposed marketing authorisation: “Olipudase alfa for treating non-Central Nervous System manifestations of Acid Sphingomyelinase Deficiency”	Thank you for your comment. The wording in the remit has been kept broad as the marketing authorisation is not yet confirmed. The committee will be able to make

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			recommendations within the marketing authorisation.
	Niemann-Pick UK (NPUK)	We agree with the remit as drafted	Thank you for your comment.
	NHS England and Improvement	The wording reflects the clinical and cost effectiveness issues	Thank you for your comment.
Timing Issues	Sanofi	We believe that NHS England will need to receive timely guidance on olipudase alfa to inform commissioning decisions and the place of this new therapy in current treatment pathways	Thank you for your comment. This evaluation has been scheduled into the work programme.
	Niemann-Pick UK (NPUK)	ASMD Niemann-Pick disease imposes a major burden upon patients, their families, health services and society. ASMD is a chronic progressive and life shortening disease. Consequently, access to effective therapies are time critical to prevent early death and irreversible disease burden. It would be unethical to delay this evaluation.	Thank you for your comment. This evaluation has been scheduled into the work programme.
	Genetic Alliance UK	This treatment is seen as a life transformative treatment for those affected by Niemann-Pick disease therefore there is urgency to progress this appraisal without delay.	Thank you for your comment. This evaluation has been scheduled into the work programme.

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	NHS England and Improvement	Not urgent	Thank you for your comment. This evaluation has been scheduled into the work programme.
Additional comments on the draft remit	Sanofi	None	Thank you.

Comment 2: the draft scope

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Background information	Sanofi	The document cites birth prevalence estimates that lead to a conclusion that "around 240 people are born with Niemann-Pick type B per year in England and Wales". We believe this grossly overestimates the number of patients with this condition, as from conversations with clinical experts, there are currently approximately 35-40 patients diagnosed with ASMD in the UK. There are currently no published studies of ASMD epidemiology in the UK. As it is an inherited, recessive disease, the epidemiology can vary substantially between populations and countries (1). A similar trend is seen in other lysosomal storage diseases, such as Pompe and Gaucher disease, where the disease prevalence in the UK is substantially lower than could be expected based on published literature (1), despite treatment being available for a number of years and the resulting increased disease awareness. There may be a number of reasons for this discrepancy between published estimates from other countries and the actual disease epidemiology in the	Thank you for your comment. The background section and the data on prevalence of the disorder has been updated to reflect the feedback heard at the scoping workshop.

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		UK. These include the genetic composition of the population, diagnostic methods used in the study (including newborn screening (2), not currently available in the UK) and the considerable variation in the phenotype of patients with the same genotype (3, 4).	
	Niemann-Pick UK (NPUK)	Adequate	Thank you for your comment.
	Genetic Alliance UK	Conversations with Niemann-Pick UK have stressed the burden of symptoms. For example, the lack of energy and fatigue experienced by individuals means that they often struggle to take part in social activities and for affected children, moving between classrooms can be exhausting and therefore they require rests and extra time to move around the school in between each lesson and are often too tired to do homework. The swelling of the belly in small children due to an enlarged liver and spleen leads to difficulties in buying clothes that fit and may result in bullying from other children that will go on to have detrimental impacts on a child's emotional wellbeing. We think the background should be expanded to cover the importance of these symptoms to people living with the condition.	Thank you for your comment. The background section has been updated to include fatigue as an important symptom. Enlargement of organs is also included as an example of the symptoms associated with this disorder. The background of the scope is intended to provide a brief overview of the condition, therefore no further changes have been made.
	NHS England and Improvement	This is accurate	Thank you for your comment.

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The technology/ intervention	Sanofi	We would suggest adding the following description of olipudase alfa trials: "The olipudase alfa clinical development programme was designed to investigate its efficacy and safety in children and adults with ASMD. The pivotal phase 3 randomised controlled double-blind trial ASCEND compared olipudase alfa with placebo in adults with ASMD type B and A/B. The phase 1/2 ASCEND-Peds study investigated olipudase alfa in children with ASMD type B and A/B. There is an ongoing extension of both trials that collects long-term data on efficacy and safety of olipudase alfa in paediatric and adult patients." This section also states "Olipudase alfa (brand name unknown, Sanofi Genzyme)". The text should read "Olipudase alfa (brand name unknown, Sanofi)".	Thank you for your comment. The technology section has been updated to include some further information on the trials available. The name of the manufacturing company has been updated.
	Niemann-Pick UK (NPUK)	No comment	Thank you.
	NHS England and Improvement	This is accurate	Thank you for your comment.
Population	Sanofi	We believe the population in the scope of the appraisal is defined appropriately based on the current anticipated licensed indication.	Thank you for your comment.
	Niemann-Pick UK (NPUK)	Although the population is defined appropriately and in keeping with current understanding, there are several factors that account for lower actual numbers. ASMD is life limiting, therefore patients don't have normal life spans, others may have milder disease with delayed diagnosis or be misdiagnosed (most often Gaucher Disease). Even allowing for these factors	Thank you for your comment. The background section and the data on prevalence of the disorder has

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		and considering that NPUK supports approx. 90% of known UK patients (37), we believe there is likely to be fewer than 100 patients in the UK.	been updated to reflect the feedback heard at the scoping workshop. No changes based on prevalence are needed in the population section of the scope.
	Genetic Alliance UK	A clarification on how the population size of Niemann-Pick disease was estimated would be appreciated. The scope estimates that 240 babies are born with Niemann-Pick type B disease each year in England and Wales (with type B being more prevalent that Type A) however, we believe this to be a significant overestimate. We have been informed by our members Niemann-Pick UK that they are aware of 37 patients in the UK with all forms of Niemann-Pick disease, 9 of which have been diagnosed in the last 5 years. Niemann-Pick UK inform us that there is likely to be fewer than 100 patients in the UK. We understand that there is some confusion with Niemann-Pick disease being misdiagnosed as Gaucher's disease however this is not a frequent misdiagnosis that can justify the overestimated population size.	Thank you for your comment. The background section and the data on prevalence of the disorder has been updated to reflect the feedback heard at the scoping workshop.
	NHS England and Improvement	The population is appropriate	Thank you for your comment.
Comparators	Sanofi	As indicated in the draft scope, best supportive care is the only option currently available for ASMD patients.	Thank you for your comment.

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	Niemann-Pick UK (NPUK)	There are currently no treatment options for ASMD except supportive care. For patients, this means their multiple and long term healthcare needs involve regular monitoring and screening tests through specialist teams. Treatments involve symptomatic relief of the disease (e.g. pain relief for bone pain) the management of the complications of the disease, (e.g. blood transfusion following bleeding episodes, management of cardiovascular disease). Because of the multisystemic nature of the disease typically many specialities are involved (cardio/respiratory team, endocrine team, haematology, hepatology - symptomatic treatments, including local and specialist teams and others physio, dietetic etc.)	Thank you for your comment. The comparator in the scope is best supportive care and is broad to allow consideration of the variety of treatment options which may be offered in current care.
	NHS England and Improvement	These are the correct comparators	Thank you for your comment.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	Sanofi	We believe that: • In addition to liver function, liver volume should also be included. • Change in physical observations is defined too broadly and in accordance with clinical monitoring guidelines this should focus on examination of the eyes, nose, heart, lungs, bone marrow, joints, weight, and height (5). • Change in neurological observations will not be an informative outcome, as olipudase alfa is anticipated to be indicated for non-central nervous system manifestations of ASMD. Neurological outcomes were measured in the clinical trials, however only as part of the safety assessment.	Thank you for your comment. Liver volume and height in children have been added to the outcomes listed. The examples listed here for change in physical observations and change in biomarkers have been added to the scope. No outcomes have been removed from the scope to keep

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		• Change in the following biomarkers should be considered within the scope of the appraisal: biomarkers C-reactive protein, ceramide, cardiac troponin, ferritin chitotriosidase, CCL18 levels, lysosphingomyelin, oxysterols (6), and lipid profile (5) • Height in children needs to be added to the scope (5).	the outcome list broad and allow all relevant outcomes to be considered during the evaluation.
	Niemann-Pick UK (NPUK)	Outcomes should be clearly listed in line with recommended guidelines on standards of care and consideration given as to how to monitor change over time. The most important outcomes from the patient perspective are achieving improved quality of life, through: decreased fatigue, improved breathing, decreased organ size leading to decreased abdominal girth (improved body image, reduced early satiety) and reduced risk of spleen rupture, addressing delayed puberty and slow growth and improved psychosocial status. The psychosocial impact for patients is a major factor and includes negative body image due the large organ size, leading to 'feeling different'.	Thank you for your comment. Health-related quality of life has been included in the scope which covers the outcomes described here. However, it was noted at the scoping workshop that fatigue and exercise intolerance, onset of puberty and growth were particularly important outcomes, therefore these have been specifically listed in the scope.
	NHS England and Improvement	Yes	Thank you for your comment.
	Sanofi	No comments	Thank you.

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Equality and Diversity	Niemann-Pick UK (NPUK)	No issue identified	Thank you for your comment.
	NHS England and Improvement	No additional equality considerations	Thank you for your comment.
Other considerations	Sanofi	None	Thank you.
	Niemann-Pick UK (NPUK)	Early diagnosis and treatment for patients with clinically detectable disease will prevent significant and irreversible burden of disease, reduce comorbidity and mortality. Currently there is no routine screening for ASMD as part of the UK's newborn screening programme. To enable the full benefit of this treatment, inclusion in the NBS programme is recommended. In addition, careful consideration should be given to the management of patients currently receiving olipudase alfa post trial and in the period leading up to and post the NICE appraisal decision process.	Thank you for your comment. Diagnosis and management of trial participants following the evaluation outcome is outside the remit for this evaluation. No changes have been made to the scope.
	Genetic Alliance UK	Treatment has been seen to be more effective the earlier it is started after diagnosis however there is no routine screening for Niemann-Pick disease as part of the newborn screening programme. It would be a shame for the full potential of this treatment for individuals to be missed due to delayed diagnosis. We encourage early engagement with the UK NSC.	Thank you for your comment. Diagnosis is outside the remit for this evaluation. No changes have been made to the scope.
Innovation	Sanofi	As the first and only disease-modifying treatment for ASMD, olipudase alfa represents a major step-change in the management of this condition. Current treatment is limited to palliative care and symptom management (7). In clinical trials olipudase alfa has been shown to improve important disease	Thank you for your comment. The committee will consider the innovative nature of

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		outcomes including spleen and liver volume, lung function and improves growth in children. (8, 9) Therefore it has the potential to become standard of care for eligible patients with ASMD.	this technology during the evaluation.
	Niemann-Pick UK (NPUK)	Olipudase alfa is the only disease modifying treatment option for ASMD patients and has the potential to make a significant impact on their health outcomes. Symptoms of the disease are debilitating and life limiting, preventing or severely limiting participation in normal daily activities. In addition, patients require multi-specialist support, testing and regular monitoring. Olipudase alfa not only appears to halt progression but reverses many aspects of the disease. With early treatment that prevents irreversible disease, patients are no longer exhausted, can attend school /work for a full day, eat normal size meals, walk greater distances without breathlessness, contribute to society and have the energy to enjoy family or social life. Furthermore, they should expect to have a far greater life expectancy.	Thank you for your comment. The committee will consider the innovative nature of this technology during the evaluation.
	NHS England and Improvement	Yes this is a step change as current care is supportive	Thank you for your comment. The committee will consider the innovative nature of this technology during the evaluation.
Questions for consultation	Sanofi	**How many people are currently being treated for Niemann-Pick disease types A and B in England?** From conversations with clinical experts, we believe there are approximately 35-40 patients with ASMD type B or A/B in the UK.	Thank you for your comment. The background section and the data on

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		Have all relevant comparators for olipudase alfa been included in the scope? Which treatments are considered to be established clinical practice in the NHS for Niemann-Pick disease types A and B? Yes, there is currently no treatment available for ASMD and the only available approach is to manage the disease symptoms. **How should best supportive care be defined?** Current management of ASMD aims to lessen the impact of individual symptoms with treatments, interventions, and lifestyle modifications designed to reduce morbidity and disease complications and improve patient quality of life. Dependent on individual symptoms treatments can include: liver (nonselective beta-blockers, ammonia, antibiotics, liver transplant), lungs (vaccinations, oxygen therapy, bronchodilators, bronchial lavage, lung transplant), cardiac (medications for valvular insufficiency, statins & surgical management) and haematology (packing & cauterization) (5, 10, 11). **Are the outcomes listed appropriate?** Please see comments above. **Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?** Patients with paediatric onset of ASMD should be considered as a separate subgroup due to the potentially more severe course of disease and different outcomes that need to be taken into account (for example growth) (5, 12, 13).	prevalence of the disorder has been updated to reflect the feedback heard at the scoping workshop. The comparator in the scope is best supportive care and is broad to allow consideration of the variety of treatment options which may be offered in current care. The outcomes in the scope have been amended based on consultation comments and feedback heard at the scoping workshop. No subgroups have been included in the scope. This is based on feedback heard at the scoping workshop that most people are

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			diagnosed during childhood and that a clinical distinction based on disease severity would be difficult to make.
	Niemann-Pick UK (NPUK)	**How many people are currently being treated for Niemann-Pick disease types A and B in England?** NPUK currently support 37 ASMD patients 35 type B (17 Children, 18 Adults) and 2 type A. **Have all relevant comparators for olipudase alfa been included in the scope?** Yes **Which treatments are considered to be established clinical practice in the** **NHS for Niemann-Pick disease types A and B?** Symptomatic relief and best supportive care **How should best supportive care be defined?** Best supportive care is complex and costly and involves regular monitoring and screening tests through specialist teams plus involvement of many others specialities such as cardio/respiratory team, endocrine team, haematology, hepatology, physio and dietetic with symptomatic treatments provided where possible. High costs are incurred through regular reliance on health systems for this progressive disease. **Are the outcomes listed appropriate?** Yes. From the patient perspective, key outcomes are:	Thank you for your comment. The background section and the data on prevalence of the disorder has been updated to reflect the feedback heard at the scoping workshop. The comparator in the scope is best supportive care and is broad to allow consideration of the variety of treatment options which may be offered in current care. The outcomes in the scope have been amended based on

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		• improved quality of life • decreased fatigue • decreased shortness of breath • decreased psychosocial impacts (allows children to participate in regular school activities, decreased abdominal girth and risk for liver/spleen rupture allows children to participate in school activities) • decreased perceived risk (of spleen rupture) which can be a barrier in some situations • improved self image due to decrease in abdominal girth	consultation comments and feedback heard at the scoping workshop.
Additional comments on the draft scope	Sanofi	We agree the HST process is the most appropriate for appraisal of olipudase alfa. We also believe it may be a suitable candidate for a managed access agreement or inclusion in the Innovative Medicines Fund.	Thank you for your comment. This topic will be evaluated through the Highly Specialised Technology Assessment process.