National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Sebelipase alfa for treating Wolman disease ID3995

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	Birmingham Women's and Children's NHSFT	Yes appropriate. This is a highly effective treatment for an otherwise fatal condition.	Thank you for your comment. No changes to the scope are needed.
	Children's Liver Disease Foundation	Yes – access to a licensed, effective treatment for babies with Wolman Disease could be life changing for affected children and their families	Thank you for your comment. No changes to the scope are needed.
	The MPS Society	Appropriate	Thank you for your comment. No changes to the scope are needed.
	University Hospitals	Yes, currently there is no licensed treatment available for LAL-D or Wolman Disease patients in the NHS	Thank you for your comment. No changes

Section	Consultee/ Commentator	Comments [sic]	Action
	Birmingham NHS FT		to the scope are needed.
	NHS England & Improvement	Yes	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	We are disappointed that the previous HST appraisal process for sebelipase alfa (ID737), which has been ongoing since 2015, has been terminated by NICE and this new appraisal (ID3995) process has been initiated without ID737 having been satisfactorily concluded. Following receipt of the notification from NICE Topic Selection of the decision to route sebelipase alfa to this second HST appraisal process on 7 September 2021, we lodged an appeal notice to the decision on 14 September 2021. In that appeal notice, we requested copies of the documentation considered by the Topic Selection Committee that formed the basis of discussions plus details of the rationale cited in the meeting for the topic referral decision. We were advised by NICE that as this topic is a narrowing of the previous appraisal, it did not proceed through the standard topic selection process and therefore no briefing note was developed. No documentation or details of the rationale for the Topic Selection Committee's routing decision has been provided and no formal response to our appeal of the routing has been received by Alexion. Alexion maintains that there is an open commercial offer for sebelipase alfa that was made to NHS England in June 2020 that has been acknowledged by NHS England but has neither been accepted nor refused. Alexion believes that while that offer is open, the termination of ID737 was premature and ID3995 should not have been initiated. We believe there has been a significant deviation from normal process at	Thank you for your comment. No changes to the scope are needed. ID737 was paused for commercial consideration and has since been affected by delays including those caused by the COVID-19 crisis. We can confirm that ID737 has not been terminated, but will remain paused until the conclusion of ID3995. Furthermore, Alexion AstraZeneca Rare Disease, NICE and NHE England have met to discuss the proposed commercial offer.

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		NICE and NHS England both in relation to ID737 and the initiation of ID3995 and we remain in contact with both agencies to try to resolve this unsatisfactory situation.	Further discussions are ongoing.
Wording	Birmingham Women's and Children's NHSFT	Not fully. The use of the terms "Wolman Disease" and "Cholesteryl Ester Storage Disease" is not clinically correct as we now appreciate this condition does not present as two distinct entities but much rather a spectrum, albeit one with a greater abundance of patients at the extremes of that spectrum. We have experienced patients being diagnosed outside the first 6 months of age but with a severe multisystem disease that is highly responsive to this therapy and who might potentially be excluded by the rigid definition proposed. We prefer: *"To evaluate the benefits and costs of sebelipase alfa within its marketing authorisation for treating severe paediatric lysosomal acid lipase deficiency for national commissioning by NHS England."* Also suggest allowing treating centres to make a clinical decision on whether a paediatric patient is severe enough to benefit from sebelipase alfa.	Thank you for your comments. At the scoping workshop, it was agreed that 'Wolman disease' is the correct wording to use to describe the population. The disease definition was also discussed and more clearly defined. This has been described in the background section of the scope.
	The MPS Society	How does the remit fit / compare to the previous evaluation? It is important to discuss classification for the Wolman's population, so as not to exclude eligible pts. There is also a need to discuss treatment for children who may fall outside of the Wolman's classification, who have a rapidly progressive fatal variant of the disease and would benefit from treatment.	Thank you for your comments. At the scoping workshop, it was agreed that 'Wolman disease' is the correct wording to use to describe the population. The disease definition was also discussed and more clearly defined. This has been described in

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			the background section of the scope.
	University Hospitals Birmingham NHS FT	Yes	Thank you for your comment. No changes to the scope are needed.
	NHS England & Improvement	Yes	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	The marketing authorisation for sebelipase alfa is broader than the Wolman population. It is therefore a misrepresentation to suggest in the draft remit wording that the benefits and costs of sebelipase alfa will be evaluated 'within its marketing authorisation'. We propose that the wording used should clearly reflect that the draft remit for ID3995 covers a more restricted population (Wolman Disease patients) than the marketing authorisation, which covers patients of all ages with LAL deficiency.	Thank you for your comment. The remit has been updated to remove 'within its marketing authorisation' and therefore avoid confusion.
Timing Issues	Birmingham Women's and Children's NHSFT	Urgent –therapy has been licensed for some time and a final decision on its commissioning in England is long overdue	Thank you for your comment. No changes to the scope are needed.
	Children's Liver Disease Foundation	The evaluation and potential access to a safe, effective treatment will save lives and is a priority	Thank you for your comment. No changes to the scope are needed.

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	The MPS Society	This technology needs reviewing urgently as it has been under a NICE evaluation since 2015. EMA approval granted in 2015.	Thank you for your comment. No changes to the scope are needed.
	NHS England & Improvement	Not urgent	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	An appraisal of sebelipase alfa (ID737) has been ongoing since 2015 and not satisfactorily resolved, if ID3995 is to proceed, then it is imperative that the appraisal process proceeds far more rapidly than a typical HST process, which typically takes over a year. Patient groups, their representatives and their clinicians have already been waiting over 6 years for a decision on reimbursement of sebelipase alfa. Initiating a whole new HST appraisal process will lead to further significant delay without application of an abbreviated approach to the submission and an abbreviated/fast track appraisal process. Should it not prove possible to satisfactorily conclude ID737 and therefore ID3995 must proceed, Alexion is prepared to work with NICE to expedite the appraisal process in whatever ways are possible.	Thank you for your comment. No changes to the scope are needed.
Additional comments on the draft remit	NHS England & Improvement	Note SMPC does indicate that a further dose escalation up to 5 mg/kg should be considered in case of suboptimal clinical response. It would be useful to have clarity on the dosage that will fall under the remit of the NICE review.	Thank you for your comment. No changes to the scope are needed.
	The MPS	It is important to discuss classification for the Wolman's population, so as not to exclude eligible pts. There is also a need to discuss treatment for children	Thank you for your comments. At the

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	Society	who may fall outside of the Wolman's classification, who have a rapidly progressive fatal variant of the disease and would benefit from treatment.	scoping workshop, it was agreed that 'Wolman disease' is the correct wording to use to describe the population. The disease definition was also discussed and more clearly defined. This has been described in the background section of the scope.

Comment 2: the draft scope

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Background information	Birmingham Women's and Children's NHSFT	See above – Wording	Thank you for your comments. The disease definition was updated after consultation and has been more clearly described in the scope.
	The MPS Society	A lot of information has been shared already with the committee. It would be important to know what additional information the committee need and the scope of the evaluation (is it going to be a full review of all data or just an update)?	Thank you for your comment. No changes to the scope are needed. The Public Involvement Programme team at

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			NICE have been in contact to outline the types of new information that would be most useful to receive.
	NHS England & Improvement	Accurate and complete	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	Largely accurate, but we would suggest the following amendments: 1. Paragraph 2, sentence 1: suggest adding the bolded text for clarity: LAL deficiency is sub-classified as Wolman disease **when it presents** in babies and cholesteryl ester storage disease **when it presents** in children or adults. 2. paragraph 2, sentence 2: suggest elaborating on the symptoms and presentation of the disease description as follows: Babies presenting with Wolman disease experience a rapidly progressive condition characterised by **intestinal failure and severe malabsorption,** growth failure, **hepatosplenomegaly and progressive** liver fibrosis and cirrhosis, normally resulting in death in the first 6 months of life, usually due to multiple organ failure. (Reference: Potter, J. E., Petts, G., Ghosh, A., White, F. J., Kinsella, J. L., Hughes, S., ... & Wynn, R. F. (2021). Enzyme replacement therapy and hematopoietic stem cell transplant: a new paradigm of treatment in Wolman disease. Orphanet Journal of Rare Diseases, 16(1), 1-14.) 3. paragraph 3, sentence 2: appears to be an overestimation; based	Thank you for your comments. The disease definition, symptoms, number of cases per year, incidence rate and status of ID737 were updated after consultation.

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		on Alexion's experience in the UK over the past 5+ years, **only 1-2 babies with Wolman Disease are born every 1-2 years**. (Source: Alexion data on file) 4. paragraph 5, sentence 1: We consider the inclusion of this statement to be inappropriate at present given commercial discussions in relation to appraisal ID737 have not yet been satisfactorily concluded and the appraisal has not yet been formally terminated. We would therefore ask that NICE updates this sentence in the Final scope, depending on the outcomes of ongoing discussions related to ID737.	
The technology/ intervention	Birmingham Women's and Children's NHSFT	Yes	Thank you for your comment. No changes to the scope are needed.
	The MPS Society	Appropriate	Thank you for your comment. No changes to the scope are needed.
	NHS England & Improvement	Accurate description	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	Yes	Thank you for your comment. No changes to the scope are needed.

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Population	Birmingham Women's and Children's NHSFT	See above – Wording	Thank you for your comments. The disease definition and population were updated after consultation and has been more clearly described in the scope.
	Genetic Alliance UK	We believe the eligible population needs further clarity. The boundary between Wolman disease and CESD is not distinct and there may be significant overlap. We understand from our members, the MPS society that some affected children have been seen to show symptoms of Wolman disease as a baby but may not be diagnosed until after the age of 12 months. It would therefore be unfortunate if this population were to be excluded from this treatment on the basis of a poorly defined boundary that doesn't account for the spectrum of the condition.	Thank you for your comments. The disease definition and population were updated after consultation and has been more clearly described in the scope.
	The MPS Society	It is important to discuss classification for the Wolman's population, so as not to exclude eligible pts. There is also a need to discuss treatment for children who may fall outside of the Wolman's classification, who have a rapidly progressive fatal variant of the disease and would benefit from treatment	Thank you for your comments. The disease definition and population were updated after consultation and has been more clearly described in the scope.
	University Hospitals Birmingham	Sebelipase alfa is licensed for LAL-D, Wolman is not mentioned in the SmPC. The technology is selecting a subgroup of patients with a more severe form of LAL-D	Thank you for your comment. No changes to the scope are

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	NHS FT		needed.
	NHS England & Improvement	Defined appropriately	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	Target population could include all patients whose LAL deficiency becomes apparent when they are babies up to the age of 24 months; this represents the population recruited in the sebelipase alfa clinical trials. We do not believe that there are sub-groups within this population which should be considered separately.	Thank you for your comments. The disease definition and population were updated after consultation and has been more clearly described in the scope.
Comparators	Birmingham Women's and Children's NHSFT	This is not well described. I would argue that "established clinical care" currently includes sebelipase alfa as most infants diagnosed recently have been treated either on clinical trials or through the company's global access to medicines scheme. The NICE evaluation committee should be under no illusion that by recommending NOT to commission sebelipase alfa routinely, a cohort of children will likely have their life saving treatment taken away from them and newly diagnosed patients will not have access to any disease-modifying therapy at present. Therefore the comparator should really be *"Palliative Care only"*	Thank you for your comments. The comparator in the scope, 'established clinical practice without sebelipase alfa', captures other supportive or palliative treatments that may be used. No changes to the scope are needed.
	The MPS Society	Appropriate	Thank you for your comment. No changes to the scope are

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			needed.
	University Hospitals Birmingham NHS FT	As no other licensed treatment available, established clinical practice without sebelipase alfa is the only treatment	Thank you for your comments. No changes to the scope are needed.
	NHS England & Improvement	Supportive care should be used as a comparator. Hematopoietic stem cell transplant (HSCT) and liver transplant should also be used as comparators but the time lag until the point at which either treatment is a clinically viable option (and during which supportive care is provided) needs to be considered.	Thank you for your comments. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	Current clinical practice in the UK involves treating Wolman Disease patients with sebelipase alfa provided by Alexion on a compassionate use basis as no other effective treatment options are available. Prior to the availability of sebelipase alfa, Wolman Disease babies would have been treated with best supportive care (BSC) to manage the symptoms of disease, comprised of • nutritional support (low fat diet, enteric/parenteral administration) • corticosteroids and mineralocorticoid replacement (for adrenal corticol insufficiency) • haematopoietic stem cell transplantation (HSCT) • liver support and/or transplantation. HSCT was associated with high procedure-related mortality in Wolman Disease patients due to disease progression and disease-associated morbidities.	Thank you for your comments. The comparator in the scope, 'established clinical practice without sebelipase alfa', captures other supportive or palliative treatments that may be used. No changes to the scope are needed.
Outcomes	Birmingham	This is a comprehensive list of outcomes relevant to long-term follow-up and	Thank you for your

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	Women's and Children's NHSFT	important to capture and describe. However, if the comparator is *"palliative care"* then the majority of these outcomes are not relevant, probably only mortality and quality of life are relevant). A long term outcome that is missing is *neurological development of children*.	comments. Your comments were discussed at the scoping workshop and the outcomes section was updated after consultation.
	The MPS Society	Early problems often involve an inflammatory process, hepatic dysfunction, severe gastrointestinal disturbance and growth failure. In the longer term nutritional and gastrointestinal problems remain the dominant feature of the disease. Liver transplant would not be appropriate for the infantile population.	Thank you for your comments. Your comments were discussed at the scoping workshop and the outcomes section was updated after consultation.
	NHS England & Improvement	Does the measure 'body weight and nutritional parameters' include growth? Does the measure 'liver disease progression' include hepatomegaly? Many of the symptoms of liver dysfunction (such as steatorrhea, nausea and vomiting) can be very debilitating for patients and carers and their impact needs to be captured. Need for liver transplant could be differently worded as need tends to indicate ability to benefit which could apply to many patients – should this be 'reduction in liver transplant numbers'. Adverse events needs to include anti drug antibodies and their impact.	Thank you for your comments. Your comments were discussed at the scoping workshop and the outcomes section was updated after consultation.
	Alexion AstraZeneca	Outcome measures could match those captured in the sebelipase alfa clinical trial programme in Wolman Disease patients as follows:	Thank you for your comments. Your

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	Rare Disease	• survival/mortality • growth (body weight) • nutritional status (number of participants with stunting, wasting, or underweight) • liver function (serum transaminases) • haematological parameters (serum ferritin, need for blood transfusions) • adverse effects of treatment In addition, we would agree with the proposal to include health-related quality of life outcomes (for patients and carers). While the following parameters are not directly relevant for the Wolman Disease population, they may provide valuable information for the long term follow up of treated patients who survive beyond infancy. It should be noted, however, that no adrenal gland function evidence was captured in sebelipase alfa clinical trials: • adrenal gland function • lipid parameters, cardiovascular events and need for liver transplant.	comments were discussed at the scoping workshop and the outcomes section was updated after consultation.
Equality and Diversity	The MPS Society	As above, it is important to discuss and clarify who would typically fall within a Wolman classification and not to exclude critically ill children from the discussions. It would be important to know what additional information the committee would need for this evaluation. Whilst the evaluation for the Wolman's population has 'superseded' the existing evaluation. It is vital to have a clear communication from NICE explaining this to the population the review is no longer relevant too.	Thank you for your comments. The disease definition and population were updated after consultation and has been more clearly described in the scope.

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	University Hospitals Birmingham NHS FT	It should include all patients with LAL-D, not only those with Wolman disease	Thank you for your comment. No changes to the scope are needed.
	NHS England & Improvement	No additional issues	Thank you for your comment. No changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	The aim of promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between all, is aligned with Alexion's principles on Diversity, Inclusion and Belonging. (Reference Alexion DI&B report available at: alexion_dib_impact_report.pdf Following the previous cost-effectiveness assessments conducted by NICE in ID737, the decision has been made to focus this appraisal on the treatment of patients with Wolman Disease only. The decision to target the Wolman population has been justified based on the higher potential for accrual of health benefits over the patients' lifetime which results in better cost-effectiveness in this population. However, older children, adolescents and adults with LAL deficiency, may be negatively impacted by not having access to treatment with sebelipase alfa, despite evidence of proven clinical efficacy in these groups. We have not identified any other foreseeable exclusions, limitations or adverse effects on protected individuals based on disability, gender reassignment, relationship status, pregnancy and maternity, race, religion or belief, sex, and/or sexual orientation.	Thank you for your comment. No changes to the scope are needed.
Other	The MPS	As above, important to define treating population	Thank you for your

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considerations	Society		comments. The disease definition and population were updated after consultation and has been more clearly described in the scope.
	Alexion AstraZeneca Rare Disease	Alexion has been funding sebelipase alfa treatment for all UK Wolman Disease patients as well as some paediatric and adult patients with LAL deficiency for over 5 years while ID737 has been ongoing. In addition to providing significant clinical benefit to patients (some of whom would not have survived without access to sebelipase alfa treatment) and their carers, the investment made by Alexion has also yielded substantial clinical and economic value to the NHS in England. We believe that the clinical and economic value of Alexion's investment to date should be reflected in this appraisal if it does proceed pending conclusion of discussions on ID737.	Thank you for your comment. No changes to the scope are needed.
Innovation	Birmingham Women's and Children's NHSFT	This is clearly a step-change in the management of LAL deficiency – altering a universally fatal condition into a long-term chronic disease	Thank you for your comment. No changes to the scope are needed.
	The MPS Society	This treatment is life saving and has been described as a step change in managing the condition and giving patients and families their lives back. Clinical colleague have commented that sebelipase alfa appears superior to many other ERT's and is the most effective ERT seen for many years for treating infants and young children.	Thank you for your comment. No changes to the scope are needed.
	NHS England & Improvement	This would represent a step change in care for this patient group.	Thank you for your comment. No changes

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			to the scope are needed.
	Alexion AstraZeneca Rare Disease	Sebelipase alfa is the first and only effective therapy licensed for the ultra-rare and devastating disease of LAL deficiency, including Wolman Disease. Prior to the availability of sebelipase alfa, the prognosis for babies born with Wolman Disease was invariably fatal within the first 6 months of life, with median age of death of 3.7 months (including for patients with HSCT). Reference: Jones SA, Valayannopoulos V, Schneider E, Eckert S, Banikazemi M, Bialer M, Cederbaum S, Chan A, Dhawan A, Di Rocco M, Domm J. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. Genetics in Medicine. 2016 May;18(5):452-8. Sebelipase alfa is a truly innovative treatment option that addresses the significant unmet need in Wolman Disease and represents a step-change in the management of the condition, transforming the prognosis for the most severely affected LAL deficiency population who have Wolman Disease.	Thank you for your comment. No changes to the scope are needed.
Questions for consultation	Birmingham Women's and Children's NHSFT	**How is Wolman disease defined clinically? How is it differentiated from LAL deficiency and cholesterol ester storage disease?** – see above – the differentiation is easy at extremes but very difficult for the small number of patients in the middle of the spectrum who are more severe than the traditional description of CESD yet have presented later than 6m of age so would not necessarily be considered a typical Wolman Disease. **Are people who have been diagnosed with Wolman disease as a baby, still be considered to have Wolman disease in childhood, adolescence and adulthood?** Yes – the disease characterisation is based on the severity of the enzyme defect. If enzyme replacement therapy were to be withdrawn from a child/adult treated successfully from infancy they would be expected to deteriorate very rapidly due to the severe enzyme defect. Of course there are	Thank you for your comments. The disease definition and population were updated after consultation and has been more clearly described in the scope. Your comments on outcomes were discussed at the scoping workshop and the outcomes section

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		no data to corroborate this as this is an unethical thing to do. **Would people with Wolman disease be treated with sebelipase alfa?** Not in England without a positive recommendation from NICE, They are currently receiving this compassionately from the manufacturer but only until such time as this evaluation is completed. **Would sebelipase alfa be used in the context of a highly specialised service? When would treatment be initiated?** Yes – it would be used only a existing lysosomal storage disorders highly specialised service centres (Birmingham, Manchester and GOSH in paediatrics and then any adult LSD centre for patients still on treatment at transition to adult care). **Does treatment continue indefinitely?** Yes if patients are continuing to benefit. **Are there any stopping criteria for sebelipase alfa in people with Wolman disease? Would people who have had a hematopoietic stem cell transplant be likely to continue treatment with sebelipase alfa?** There are insufficient data to answer this now but it may be possible for some patients to stop sebelipase after a successful HSCT. However experience shows that HSCT is universally unsuccessful in someone who has never received sebelipase alfa probably due to the severe burden of disease at the onset of the HSCT process. **Is hematopoietic stem cell transplantation a comparator for sebelipase alfa that should be included? Would people with Wolman disease be treated with sebelipase alfa with the aim of subsequently having a hematopoietic stem cell transplant?** No. HSCT has been universally unsuccessful in patients who have not received sebelipase alfa so for the purposes of this evaluation the comparator should be palliative care only. Whether or not a patient gets referred for HSCT after stabilising on sebelipase alfa should be for the treating centres to decide on a case-by-case	was also updated after consultation. No other changes to the scope are needed.

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		basis. **Is the need for liver transplant a relevant outcome to consider for people with Wolman disease?** No because without enzyme replacement therapy, liver transplantation would not be recommended in the first place.	
	The MPS Society	**How is Wolman disease defined clinically? How is it differentiated from LAL deficiency and cholesterol ester storage disease?** LAL deficiency is a spectrum of disease. In the past early onset in infants was referred to as Wolmans disease and late onset in children and adults Cholesteryl Ester Storage Disease. Rate of progression varies greatly. Those presenting in infancy having a more rapid rate of decline. **What is the incidence and prevalence of Wolman disease in England?** In England we have approximately 10 children. We would expect to see between 1-3 children born a year **Would people with Wolman disease be treated with sebelipase alfa?** Yes **Would sebelipase alfa be used in the context of a highly specialised service? When would treatment be initiated?** Yes, immediately after diagnosis where possible. **Is hematopoietic stem cell transplantation a comparator for sebelipase alfa that should be included?** Whilst HSCT has been used, this is not standard of care and should not be used as a comparator or viewed as 'best alternative care'. HSCT has been used as a final approach where ERT has failed. The high mortality / morbidity associated with HSCT and the absence of CNS involvement would be clinical reasons not to transplant.	Thank you for your comments. The disease definition, population, number of cases per year, incidence rate and outcomes section were updated after consultation. No other changes to the scope are needed.
	Alexion AstraZeneca Rare Disease	**How is Wolman Disease defined clinically? How is it differentiated from LAL deficiency and cholesterol ester storage disease?** Wolman disease is defined as infantile-onset, rapidly progressive LAL deficiency that leads to death most often during the first 6 months of age. In contrast, LAL-	Thank you for your comments. The disease definition, population, number of cases per

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		deficiency/cholesterol ester storage disease is usually not symptomatic in infancy, tending to only become symptomatic in childhood, adolescence or adulthood, depending on the degree of LAL deficiency. **What is the incidence and prevalence of Wolman Disease in England? Wolman Disease is defined as LAL deficiency in babies. Are people who have been diagnosed with Wolman Disease as a baby still considered to have Wolman Disease in childhood, adolescence and adulthood? What is the age range of people with Wolman Disease?** We are not aware of any published epidemiology data for Wolman Disease in the UK. Available publications reference estimated incidence of Wolman Disease range from 1:100,000 to 1 per 1,000,000 births. [redacted]. References: Aguisanda, F., Thorne, N., Zheng, W. Targeting Wolman disease and cholesteryl ester storage disease: disease pathogenesis and therapeutic development. Curr. Chem. Genomics Transl. Med. 11: 1-18, 2017. Del Angel G, Hutchinson AT, Jain NK, Forbes CD, Reynders J. Large-scale functional LIPA variant characterization to improve birth prevalence estimates of lysosomal acid lipase deficiency. Hum Mutat. 2019 Nov; 40(11):2007-2020. As indicated above Wolman Disease is the most severe, rapidly progressive form of LAL deficiency that becomes symptomatic in infancy. The severe LAL deficiency in Wolman Disease patients persists through their lives – it does not resolve and remains clinically relevant and life-threatening. As such, Wolman Disease patients who survive infancy will require lifelong treatment to address the deficiency. Currently, the oldest patient in England that started sebelipase alfa treatment as infant is 10 years old. **Would people with Wolman Disease be treated with sebelipase alfa? Would sebelipase alfa be used in the context of a highly specialised service? When would treatment be initiated?** Sebelipase alfa is the only licensed enzyme replacement therapy available for the treatment of the LAL	year, incidence rate and outcomes section were updated after consultation. No other changes to the scope are needed.

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		deficiency in patients with Wolman Disease and is therefore an appropriate treatment for these patients. Treatment of Wolman Disease patients in NHS England would fall under the already-established Lysosomal Storage Disorders Service with specialist centres in Birmingham Children's Hospital, Manchester University NHS Foundation Trust and Great Ormond Street Hospital London. Treatment with sebelipase alfa should be initiated immediately or as soon as possible following presentation and diagnosis of Wolman Disease. **Does treatment continue indefinitely? Are there any stopping criteria for sebelipase alfa in people with Wolman Disease? Would people who have had a hematopoietic stem cell transplant be likely to continue treatment with sebelipase alfa?** As the underlying LAL deficiency persists and does not resolve, lifelong treatment with sebelipase alfa is required in Wolman Disease patients. As the underlying LAL deficiency persists throughout a patient's life, treatment cessation/stopping rules are not appropriate for Wolman Disease patients. There are limited data on HSCT and sebelipase alfa. One study has been published whereby HSCT was reported to reduce the dose of sebelipase post transplant, but ongoing treatment was still required. (Reference: Potter JE, Petts G, Ghosh A, White FJ, Kinsella JL, Hughes S, Roberts J, Hodgkinson A, Brammeier K, Church H, Merrigan C. Enzyme replacement therapy and hematopoietic stem cell transplant: a new paradigm of treatment in Wolman disease. Orphanet Journal of Rare Diseases. 2021 Dec;16(1):1-4.) **Have all relevant comparators for sebelipase alfa been included in the scope? Which treatments are considered to be established clinical practice in the NHS for Wolman disease? Is hematopoietic stem cell transplantation a comparator for sebelipase alfa that should be**	

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		included? Are the outcomes listed appropriate? Are there any that should be added (or removed) to make this more relevant to Wolman disease specifically (not LAL deficiency in general)? Is the need for liver transplant a relevant outcome to consider for people with Wolman disease? Responses to most of these questions have been provided in the relevant sections above. Re HSCT: Prior to the availability of sebelipase alfa, HSCT was one treatment option for Wolman Disease patients. However, with the availability of sebelipase alfa (albeit through Alexion's compassionate use programme) in the UK, the enzyme replacement therapy (ERT) has become the standard of care for Wolman Disease patients. HSCT has recently been used after successful ERT, however, it is not clear whether this multi-modal approach to treatment is suitable for all Wolman Disease patients or whether it is likely to become incorporated into routine clinical practice. **Are there any subgroups of people in whom sebelipase alfa is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately? Would these subgroups include: people with very rapidly progressing LAL deficiency; people who may be candidates for hematopoietic stem cell transplant; people who have had a liver transplant? Would people with Wolman disease be treated with sebelipase alfa with the aim of subsequently having a hematopoietic stem cell transplant?** LAL deficiency is a very rare disease and Wolman Disease already represents the smallest subgroup of the LAL deficiency patients, representing those patients with the most severe, rapidly progressive form of the disease. We do not believe the Wolman Disease population can be further sub-categorised. Please see above response re sebelipase alfa and HSCT.	

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		Is the Highly Specialised Technologies Programme the appropriate route for this appraisal? Notwithstanding the comments made above regarding the overall appropriateness of this appraisal, if ID3995 is to proceed, Alexion firmly believes that the HST programme is the appropriate evaluation process.	
Additional comments on the draft scope	NHS England & Improvement	Sebelipase, if approved by NICE, would be delivered through a highly specialised service. There is emerging evidence that some children may not be eligible for a hematopoietic stem cell transplant (HSCT) and can successfully continue on the drug; this requires consideration. There is also evidence that children who have received HSCT still require the drug, albeit in smaller/less frequent doses. Supportive care should be used as a comparator. HSCT and liver transplant should also be used as comparators but the time lag until the point at which either treatment is a clinically viable option (and during which supportive care is provided) needs to be considered.	Thank you for your comments. The outcomes section was updated after consultation. No other changes to the scope are needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Neonatal and Paediatric Pharmacists Group (NPPG)