National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

OTL-200 for treating metachromatic leukodystrophy

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	ArchAngel MLD Trust	ArchAngel MLD Trust believes that this is an entirely appropriate referral to NICE, given the severity of the condition and the current absence of any treatment for MLD patients other than palliative or supportive.	Comment noted. The evaluation has been scheduled into the Highly Specialised Technologies work programme.
	Association of British Neurologists	Agree appropriate although disease is very rare in adults. Likely less than 50 adults living in the UK.	Comment noted. The evaluation has been scheduled into the Highly Specialised Technologies work programme.
	Great Ormond Street Hospital NHSFT	The remit is appropriate	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The MPS Society	Appropriate	Comment noted. No change to the scope required.
	Orchard Therapeutics	Orchard Therapeutics welcomes and is strongly in agreement that OTL-200 should be referred to NICE for appraisal under the HST process, given the high unmet need for metachromatic leukodystrophy (MLD) patients.	Comment noted. The evaluation has been scheduled into the Highly Specialised Technologies work programme.
Wording	ArchAngel MLD Trust	ArchAngel MLD Trust agrees that the wording of the document reflects the issues, excepting the following: The opening paragraph of the 'Background' section does not accurately reflect the gravity of this condition. Metachromatic Leukodystrophy is a chronically disabling and life-limiting condition. In 'Nature of the Condition' the word 'mortality' should also be included.	Comment noted. The background section has been updated in the light of the comments received.
	Association of British Neurologists	Agree.	Comment noted. No change to the scope required.
	Great Ormond Street Hospital NHSFT	The wording Is appropriate	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The MPS Society	We agree that the wording reflects the issues of clinical effectiveness. We are however unclear how this technology will fit within the current cost effectiveness using incremental cost per quality-adjusted life years?	Comment noted. Technologies are evaluated using the framework as set out in the Interim Process and Methods of the Highly Specialised Technologies Programme, where the relative benefits and costs associated with the technologies (cost-effectiveness) will be taken into account. However, if appropriate, other factors such as the wider benefits not captured in QALY may be considered by the committee.
	Orchard Therapeutics	Orchard Therapeutics agrees that the wording of the remit reflects the issues of clinical and cost-effectiveness of OTL-200 for the treatment of MLD.	Comment noted. No change to the scope required.
Timing Issues	ArchAngel MLD Trust	This evaluation should be expedited considering that this technology can have potentially life-saving or life-changing effect and also that timely intervention is an important factor in its effectiveness. Lives could potentially be saved or significantly altered as soon as this technology is available.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is

Section	Consultee/ Commentator	Comments [sic]	Action
			granted. NICE has scheduled this topic into its work programme. No action needed.
	Association of British Neurologists	Other treatments, particularly for adults are high risk.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Great Ormond Street Hospital NHSFT	There is no established treatment for MLD, so there is urgent need for an effective treatment.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	The MPS Society	It is important that this technology is evaluated urgently as EMA approval has been sought, with an accelerated assessment being granted in November 2019.	Comment noted. NICE aims to provide draft guidance to the NHS

Section	Consultee/ Commentator	Comments [sic]	Action
			within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Orchard Therapeutics	MLD is a devastating life-threatening disease with a severe prognosis and extremely poor quality of life for all affected patients, especially in young children with the more aggressive forms of the disease. Currently, there are no approved pharmacological or gene therapy treatments for any MLD variant and alternatives are limited to supportive care, which cannot influence the fatal outcome of this devastating disease[1]. Treatment options investigated to date have not demonstrated significant effect on the clinical course of MLD patients. This absence of effective therapies leads to a high unmet medical need for all MLD patients, particularly in the youngest patients who suffer from the most aggressive late infantile (LI) and early juvenile (EJ) variants of the disease. In addition, due to the rapidly progressive nature of the disease there is a limited window of opportunity to treat these patients. A delay in availability could mean patients will miss their opportunity to be treated. Due to the potential health gain, this warrants access to innovative therapeutic approaches as soon as possible for the benefit of MLD patients. As such, the NICE HST appraisal of OTL-200 should be prioritised within the work programme to ensure availability coincides with the time of regulatory approval by the EU Commission.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	Association of British Neurologists	MLD, children 75% and adults 25%. Little is given on OTL-200. More detail is required. How is the gene therapy given, is this an enzyme given directly, or an adenovirus vector with the enzyme to replace the gene and protein?	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail, scope unchanged.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	ArchAngel MLD Trust	The opening paragraph of the 'Background' section does not accurately reflect the gravity of this condition. Metachromatic Leukodystrophy is a chronically disabling and life-limiting condition. The Late Infantile (predominant) sub-type causes certain death in childhood. The Early Juvenile sub-type sufferers experience the same loss of fundamental abilities, just at a less accelerated rate. Adult cases suffer incapacitating cognitive impairments. All sub-types are significantly life-altering and result in a markedly reduced life expectancy. The language used should reflect this. It is also important to note that although the document states "Children with early juvenile MLD who have a diagnosis before they have symptoms or who have only recently stated having symptoms may be able to have umbilical cord blood or stem cell transplant", we are advised by leading clinicians that this is not common practice or a typical recommendation in the UK.	Comment noted. The background section of the scope has been updated in light of the comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Neurologists	Ok but little detail	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail, no action needed.
	Great Ormond Street Hospital NHSFT	This is accurate	Comment noted. No change to the scope required.
	The MPS Society	We are not aware of HSCT being curative. HSCT may address some of the symptoms of the disease but not all. HSCT is only effective for those patients who are either pre symptomatic or early on in their disease, this is somewhat limited in this patient group. HSCT has a high mortality risk.	Comment noted. The background section of the scope has been updated in light of the comment.
	Orchard Therapeutics	We propose rewording the following sections to improve clarity. **Reword paragraph 1:** MLD is a rare autosomal recessive genetic disorder caused by mutations in the arylsulfatase A (ARSA) gene that result in deficiency of its corresponding enzyme. This deficiency causes accumulation of sulfatide in the central and peripheral nervous system, leading to loss of motor and cognitive functions and early death. Disease with earlier onset is associated with a quicker progression and more severely reduced life expectancy compared with an onset later in life.[1,2,3]	Comment noted. The background section of the scope is intended only to briefly describe the disease, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The background section has been

Section	Consultee/ Commentator	Comments [sic]	Action
		Reword paragraph 2: The MLD disease spectrum can present in a variety of clinical forms primarily based on the arbitrary criterion of age of onset of the first symptoms of the disease, rather than biological and clinical parameters. At least three clinical forms of the disease are commonly described (Late Infantile, Juvenile, and Adult)[4,5], and the underlying disease pathophysiology is common for all phenotypic forms of MLD. The arbitrary classification of MLD is particularly applicable to the stratification of Juvenile forms into Early and Late Juvenile. Regardless of the clinical classification, the clinical course of the disease can be broadly divided into a pre-symptomatic stage with normal motor and cognitive development, followed by onset of first symptoms and a period of developmental plateau, which is short in early onset forms and longer and more variable in late onset forms. The disease inevitably ends in a decerebrated state and eventually death for all phenotypic forms of the disease.[1,6,7] In the most common form, Late Infantile MLD, most patients will die before the age of 5 (5-year survival rate of 25%). The survival rates at 5 and 10 years for the juvenile form are 70% and 44%, respectively.[8] **Reword paragraph 3:** The incidence of MLD is approximately 1.1 cases per 100,000 livebirths in the European Union (EU).[9-14] One leading UK centre estimates the incidence in the UK to be approximately 1:40,000 live births[15]. It is possible that the incidence may prove to be higher when newborn screening becomes available.[16] European studies suggest that approximately 40% to 60% of patients have the LI variant, 20% to 40% have the Juvenile variant and approximately 18% to 20% have an adult variant.[3,9,13,17,18] **Reword paragraph 4:** There is currently no curative treatment for MLD. Available treatments only address the symptoms of the disease and not the underlying pathophysiologic mechanisms, and none of therapeutic approaches have proven to influence the fatal outcome.	updated in line with some of the comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		Allogeneic hematopoietic stem cell transplantation (HSCT) has been used for the treatment of MLD but results available so far have been inconsistent and are associated with risks for serious complications, such as graft-rejection, graft versus host disease (GVHD) or complications derived from intense conditioning regimens. Given the more rapid progression in early onset MLD variants, the use of HSCT has been particularly limited to MLD patients with late-onset variants where, considering the associated risks of additional conditioning and those secondary to allogenic transplantation (GVHD, engraftment failures), the benefit risk profile remains to be determined.	
The technology/ intervention	ArchAngel MLD Trust	Yes.	Comment noted. No change to the scope required.
	Association of British Neurologists	No detail	Comment noted. The technology section is intended only to briefly outline the technology. No change to the scope required.
	Great Ormond Street Hospital NHSFT	This is correct.	Comment noted. No change to the scope required.
	The MPS Society	The technology is OTL-200 not OLT-200. As MLD is a neurological condition the aim of the treatment is to target the CNS (Central Nervous System) and the PNS (peripheral Nervous System).	Comment noted. The scope has been updated.
	Orchard Therapeutics	The technology has been misspelt, it should be OTL-200 rather than OLT-200.	Comment noted. The technology section is intended only to briefly

Section	Consultee/ Commentator	Comments [sic]	Action
		We propose rewording the following section to improve clarity. **Replace paragraph 1 with:** OTL-200 (Orchard Therapeutics) is an *ex vivo* gene therapy. The active substance is defined as an autologous $CD34^+$ cell-enriched population that contains hematopoietic stem and progenitor cells (HSPCs) transduced *ex vivo* using a lentiviral vector encoding the human ARSA gene. The proposed mechanism of action of OTL-200 to correct the metabolic dysfunction in the central nervous system (CNS) and peripheral nervous system (PNS) is expected to be mediated by a fraction of the infused genetically modified cells and/or their myeloid progeny migrating into the brain across the blood-brain barrier, engrafting and partially reconstituting resident microglia in the brain and endoneural macrophages in the PNS.[19-22] After transduction with one or more working copies of the gene, engrafted genetically modified cells then synthesize ARSA enzyme at supraphysiological levels. The enzyme is secreted into the extracellular matrix and taken up by surrounding cells leading to the intracellular breakdown of harmful sulfatides and preventing their accumulation; in turn, these actions on sulfatides prevent the processes that underlie the clinical manifestations and disease progression of MLD, namely brain and PNS demyelination, neurodegeneration and atrophy.[20] Furthermore, repopulation of microglia with genetically modified cells engrafting in the brain after treatment with OTL-200 is anticipated to address inflammatory and apoptotic components mediated by microglial activation, as well as to reconstitute the scavenging microglial function aimed at removing extracellular sulfatide, key components involved in the pathogenesis of MLD across variants.[2,20,23,24]	outline the technology, it is not designed to be exhaustive in its detail. The name of the technology has been corrected.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	ArchAngel MLD Trust	Yes.	Comment noted. No changes to the scope required.
	Association of British Neurologists	No number estimate	Comment noted. Estimates of incidence and prevalence are set out in the background section of the scope. The population section of the scope defines the decision problem for the evaluation so the population size is not required. No changes to the scope required.
	Great Ormond Street Hospital NHSFT	It may be helpful to consider the different clinical presentations separately, as the rate of progression of the condition is different in these subgroups. The disease progresses rapidly in the late infantile sub group, but less so in the later-onset patients. It may not be necessary to restrict the treatment to early symptomatic groups only in the later onset juvenile and adult patients, and for some of these patients could be considered even if symptoms have been present for a number of years.	Comment noted. As noted during the scoping workshop, people with pre-symptomatic MLD will benefit most from the treatment; For those with early-symptomatic MLD, the situation is a bit more complicated. They can benefit from the treatment too but to a lesser extent.

Section	Consultee/ Commentator	Comments [sic]	Action
			Different subtypes are listed under subgroups of the population that may be considered separately if evidence allows.
	The MPS Society	Agree	Comment noted. No change to the scope required.
	Orchard Therapeutics	The population should be specified according to the proposed indication. This would be: **‘**Treatment of MLD in patients from birth to before 17 years and in older patients for whom disease onset occurred before 17 years. Treatment with OTL-200 should be performed before the disease enters its rapidly progressive phase’.	Comment noted. The population has been kept broad as people with MLD to accommodate any potential changes.
Comparators	ArchAngel MLD Trust	There is no standard treatment to hold in comparison, just best supportive care.	Comment noted. As agreed at the scoping workshop, stem cell transplant and best supportive care are the relevant comparators. Without the new technology, a small proportion of patients would still get HSCT, although this is not commonly done because of the risk of

Section	Consultee/ Commentator	Comments [sic]	Action
			morbidity and the lack of data on long-term efficacy.
	Association of British Neurologists	They mention but discuss little on current treatment	Comment noted. The comparators section of the scope is intended only to be a list of comparators that should be considered in the evaluation. No changes to the scope required.
	Great Ormond Street Hospital NHSFT	The current available treatments are correct. Neither can be described as “best alternative care”. The choice is between palliative care (the only option available to late infantile patients) and for later onset patients, HSCT is not safe and the long term efficacy is not known.	Comment noted. As agreed at the scoping workshop, stem cell transplant and best supportive care are the relevant comparators.
	The MPS Society	Agree although HSCT is rarely done in this patient group	Comment noted. As discussed at the scoping workshop, stem cell transplant would be an option for a minority of people if OTL-200 were not available, and therefore stem cell transplant and best supportive care are the relevant comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
	Orchard Therapeutics	Orchard Therapeutics agrees that the comparators listed are treatments currently used to which OTL-200 may be compared. Please reverse the order of the bullets and amend the text to read: • Best supportive care (standard of care) • Allogeneic hematopoietic stem cell transplant (only early symptomatic and/or asymptomatic) Best supportive/symptomatic care would include: • Management of dystonia • Management of infections • Management of seizures (if required) • Management of secretions • Pain relief/sedative drugs (if required) • Feeding support (including gastrostomy) • Psychological and social support (including specialist schooling) • Coordination of the multidisciplinary team and community care • Genetic advice and planning • End of life care Allogenic hematopoietic stem cell transplantation (HSCT) is occasionally applied in clinical practice for the treatment of MLD. Although HSCT is reported to have some effect in the stabilisation of some patients with the juvenile or adult forms of the disease (at the pre- or early symptomatic stages)[25,26], the outcomes are inconsistent, and currently no valid therapeutic options are available to affected patients, especially the youngest (LI) patients.	Comment noted. As discussed at the scoping workshop, although the data is limited, stem cell transplant would be an option for a minority of people if OTL-200 were not available, and therefore stem cell transplant and best supportive care are the relevant comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
		However, allogeneic HSCT is associated with significant morbidities such as infections and graft vs. host reaction due to allogenic material used and is accompanied with a risk of treatment-related mortality. Thus, allogeneic HSCT remains controversial for different reasons, particularly: • the difficulty in generalising study results due to the use of different eligibility criteria and transplantation protocols • outcome data from older cohorts are not immediately applicable for predicting current outcomes given the continuous improvement of transplant-related morbidity and mortality due to advances in donor-recipient HLA typing and matching, conditioning, infectious disease detection and management, and the use of non-carrier donors.[27] Compared to HSCT, an autologous gene therapy with OTL-200 is associated with a significantly reduced transplant-related morbidity and avoids the risks of GvHD. To date, no treatment-related SAEs nor treatment-related mortality have been reported. Therefore, the availability of a gene therapy would represent a significant advance in comparison to conventional allogeneic HSCT.	
Outcomes	ArchAngel MLD Trust	Yes. Personal experience of OTL-200 via clinical trial can testify to these outcome measures being the most important to families undergoing this treatment; stability of nerve conduction is also considered an important marker. Outcomes listed should be compared to data in the MLD natural history study.	Comment noted. The way in which the outcome should be measured is not usually specified in the scope. Stability of nerve conduction has been added to the outcomes in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Neurologists	Fine	Comment noted. No change to the scope required.
	Great Ormond Street Hospital NHSFT	Yes these are appropriate	Comment noted. No change to the scope required.
	The MPS Society	Agree, although this should be compared against Natural History data	Comment noted. The way by which the outcome should be measured or assessed is not usually specified in the scope. No change to the scope required.
	Orchard Therapeutics	Amend Bullet 1 to read: • total gross motor function • measure (GMFM) compared with historical well-matched control MLD population Amend Bullet 2 to read: • neurological function compared with historical well-matched control MLD population Amend Bullet 3 to read: • neurocognitive function compared with historical well-matched control MLD population Amend Bullet 4 to read: • change from baseline in arylsulfatase (ARSA) activity	Comment noted. The way by which the outcome should be measured or assessed is not usually specified in the scope. Age and time at severe motor impairment or death has been added to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		Amend Bullet 5 to read: • Age and time at severe motor impairment or death compared with historical well-matched control MLD population	
Economic analysis	ArchAngel MLD Trust	No comments or concerns.	Comment noted. No change to the scope required.
Equality and Diversity	Association of British Neurologists	Fine	Comment noted. No change to the scope required.
	Great Ormond Street Hospital NHSFT	No comment	Comment noted. No change to the scope required.
	The MPS Society	None	Comment noted. No change to the scope required.
	Orchard Therapeutics	None	Comment noted. No change to the scope required.
Other considerations	ArchAngel MLD Trust	Value for Money: as QALYs can be difficult to assess in rare diseases such as MLD, a comparison of cost of the technology against a per annum cost of best supportive care would also be appropriate.	Comment noted. Technologies are evaluated using the framework as set out in the Interim Process and Methods of the Highly Specialised Technologies

Section	Consultee/ Commentator	Comments [sic]	Action
			Programme, where the relative benefits and costs associated with the technologies (cost-effectiveness) will be taken into account. However, if appropriate, other factors such as the wider benefits not captured by the QALY may be considered by the committee.
	Association of British Neurologists	The detail and possible long term treatment effects need to be given in detail	Comment noted. The long-term effect of treatment should be considered in the company's submission. No change to the scope required.
	Great Ormond Street Hospital NHSFT	Nil	Comment noted. No change to the scope required.
	Orchard Therapeutics	If the evidence allows, the following subgroups may be considered according to the proposed indication: • Late infantile onset MLD • Early juvenile onset MLD • Late juvenile onset MLD	Comment noted. As discussed at the scoping workshop, the classification of juvenile MLD has not been split into early and late juvenile MLD in the

Section	Consultee/ Commentator	Comments [sic]	Action
			scope to align with the most commonly used classifications of the disease. No change to the scope required.
Innovation	ArchAngel MLD Trust	ArchAngel MLD Trust believes that this technology is remarkable. It has the potential to save or significantly alter the lives of those affected by what is essentially a terminal illness. We believe it would make a pivotal change to the health and prognosis of applicable MLD patients. The chairperson of ArchAngel MLD Trust has direct experience of OTL-200 via participation in a clinical trial and has developed close relationships with the majority of the trial cohort. They have witnessed significant alteration to the natural course of the disease in the majority of trial patients. Children who were diagnosed as a result of having an affected elder sibling are thriving and have far surpassed the life expectancy indicated by their untreated sibling. Many children who narrowly missed the inclusion criteria have long since passed away, whereas trial subjects of the same age and classification of disease have maintained a significant quality of life. Many patients known to the charity who have received OTL-200, including UK families, have zero subsequent health needs. This particular gene therapy technique is also an important innovation which may have positive influence on treatments being developed for other serious health conditions.	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.
	Association of British Neurologists	Not enough detail to give a considered opinion	Comment noted. The innovative nature of the technology will be considered throughout

Section	Consultee/ Commentator	Comments [sic]	Action
			the course of the appraisal.
	Great Ormond Street Hospital NHSFT	The technology represents a step change in the treatment of MLD and it aims to correct the underlying biochemical defect. No satisfactory treatment currently exists.	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.
	The MPS Society	This is not only the first treatment for MLD but is the first gene therapy for this condition and its related Lysosomal Storage Disorders to be put forward to NICE. The aim of this gene therapy is to correct the genetic defect in MLD patients, enabling patients to produce normal levels of enzyme. From the data presented treated patients (post 7 years) are continuing to show stabilisation of enzyme levels and little disease progression	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.
	Orchard Therapeutics	Orchard Therapeutics believes OTL-200 an innovative gene therapy targeting the root cause of the disease by correcting the genetic defect in MLD patients' own CD34+ hematopoietic stem and progenitor cells (HSPCs). OTL-200 is the first treatment indicated for MLD. and was developed according to the hypothesis that autologous cells can be genetically modified to constitutively express normal or supra-physiological levels of the therapeutic enzyme ARSA and become a more effective source of functional enzyme than wild-type donor cells in cross-correcting nearby diseased cells. Furthermore, microglia repopulation with genetically modified cells engrafting in the brain after treatment with OTL-200 is anticipated to also address inflammatory and apoptotic components mediated by microglial activation, as well as reconstitute the scavenging microglial function aiming at removing extracellular sulfatide, key components involved in the pathogenesis of MLD across variants. Patients treated with OTL-200 exhibited progressive reconstitution of ARSA levels at 2 years and continued to demonstrate durable and lasting reconstituted ARSA levels at 7 years post treatment in	Comment noted. The innovative nature of the technology will be considered throughout the course of the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		patients with that follow-up post-treatment. OTL-200 is a step-change compared to the existing standard of care and hence has significant health-related benefits in terms of quality-adjusted survival. Early-onset MLD is characterised by a rapid slowing of physical development, particularly in the LI variant. Development of motor skills slows down, and those that have already been learnt are lost. Up to 90% of children lose all motor function and become totally dependent by the age of 3 years. For this reason, stabilising or reducing progression of the disease is considered to be a clinically relevant benefit to patients and their families. Patients treated with OTL-200 showed statistically significant and clinically relevant motor score difference at 3 years post-treatment. Three years after treatment with OTL-200, the difference for LI and EJ patients' Gross Motor Function Measure (GMFM) scores was 72% and 57% versus controls, respectively. Most treated children showed normal development of cognitive skills throughout follow-up. IQ measures, such as cognitive and language abilities, complement results from the measurement of motor function, supporting the translation of high levels of engraftment and enzymatic reconstitution in peripheral blood and cerebrospinal fluid into relevant treatment effects on key symptomatic domains in MLD patients following treatment with OTL-200.	
Questions for consultation	ArchAngel MLD Trust	***How many people have pre-symptomatic late infantile MLD, pre- or early-symptomatic juvenile MLD, or adult type MLD in England? For each subtype, how many new cases are diagnosed each year in England?*** ArchAngel MLD Trust is aware of the following patients who have contacted the charity since inception in 2014: 25 living patients, comprised of: 15 Late Infantile, 6 Early Juvenile, 4 Adult;	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		14 deceased patients, comprised of: 5 Late-Infantile, 3 Early Juvenile, 6 Adult. New referrals to the charity are approximately 2 per annum. However there will be additional patients not known to the charity. We therefore do not have any reliable statistics on annual diagnoses. ***Are people with MLD (including the 3 main subtypes) routinely tested for genetic mutations? How are MLD and its main subtypes identified and diagnosed in practice? Are there variations across the country regarding the identification and diagnosis of MLD and its main subtypes?*** According to families known to ArchAngel MLD Trust, in the absence of previous family history of the disease an MLD diagnostic journey can be a difficult and unclear one. Most LI patients have been identified through failure to meet (or significant issue with) a major motor milestone. EJ patients have initially presented with some change in cognitive or coordination abilities. Adult patients predominantly exhibit with dementia type tendencies. All types seem to have been identified by brain MRI and eliminatory blood tests. Once MLD is suspected, urinary tests are undertaken to detect the presence of toxic sulfatides. Only once a diagnosis of MLD has been confirmed is genetic testing carried out, in order to identify specific mutations, of which there are over 100 known to date. All cases have been identified at their local hospital, with most cases then being referred on to a regional centre, mainly Manchester Children's Hospital and Great Ormond Street Hospital. ArchAngel MLD Trust is spearheading a Newborn Screening campaign for MLD, which if successful will allow timely identification of more patients who could benefit from this transformative technology. Approval of this technology will be an important step towards newborn screening approval.	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Would OTL-200 be offered for pre-symptomatic late infantile MLD, pre- or early-symptomatic juvenile MLD, or also for MLD in adults? To our knowledge, this technology has not yet been developed for adult cases. ***Would OTL-200 be offered to people with MLD and who have had stem cell transplant?*** To our knowledge, this treatment would not be offered to patients whom have already received stem cell transplants. ***How are the services for pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or adult type MLD organised in the NHS? Is it expected that OTL-200 would be delivered within the existing framework of services, or would new treatment centres be required?*** All sub-types of MLD are currently managed within the NHS via Neuro-disability and Metabolic consultants at regional centres, who filter advice to local community teams. The 6 UK children who have already received OTL-200 as part of a clinical trial are currently managed within this existing framework (or have no subsequent related health needs). The clinical trial at Ospedale San Raffale in Milan was conducted within a standard bone marrow transplant unit. We believe this technology would likely be carried within an existing UK framework at a major UK transplant centre.	Comment noted. No change to the scope required. Comment noted. No change to the scope required. Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for OTL-200 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for MLD? How should best supportive care be defined? ArchAngel MLD Trust is connected to over 400 MLD families world-wide and is a member of the global collaborative Cure MLD. From this knowledge base, it is our opinion that the only relative comparator to OTL-200 is best supportive care, i.e. management of fundamental symptoms including hypertonia, impaired swallowing, seizures, respiratory infections, secretions, paralysis, dementia. ***Are there any other subgroups of people in whom OTL-200 is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?*** ArchAngel MLD Trust is not aware of any sub-groups other than those listed which could benefit from this technology. ***NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf).*** ArchAngel MLD Trust believes that evaluation of this technology through the NICE Highly Specialised technology programme is the most appropriate	Comment noted. As agreed at the scoping workshop, best supportive care and stem cell transplant are the relevant comparators. Comment noted. No change to the scope required. Comment noted. The evaluation has been scheduled into the Highly Specialised Technologies work programme. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		process, given the severity of the condition and the absence of any treatment other than palliative or supportive.	
	Association of British Neurologists	More details on OTL-200 are needed and comparison with current treatment	Comment noted. The scope is intended only to be a brief overview of the disease area, technology, and an outline of the decision problem. No change to the scope required.
	Great Ormond Street Hospital NHSFT	**How many people have pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or adult type MLD in England? For each subtype, how many new cases are diagnosed each year in England?** Difficult to estimate the correct number of asymptomatic patients in the absence of pre-symptomatic screening. There may be existing siblings of previous patients when antenatal screening has not bee undertaken. Estimated number of new diagnoses per year: Late infantile: 5-6; Juvenile: 2-3; Adult unknown	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are people with MLD (including the 3 main subtypes) routinely tested for genetic mutations? How are MLD and its main subtypes identified and diagnosed in practice? Are there variations across the country regarding the identification and diagnosis of MLD and its main subtypes? Genetic confirmation is routinely carried out. The diagnosis is usually made through paediatricians and neurologists when patients present with developmental delay, learning problems, or behavioural problems. Usually the diagnosis is relatively quick in the late infantile form, but may be delayed in the later onset forms as the symptoms can be non specific. Once MLD is suspected, the diagnostic pathway is straightforward as the enzyme test is readily available in specialist labs. Referral to the tertiary Lysosomal Storage Disease (LSD) centres is made once the diagnosis is established, even if it is for a one-off opinion. Long term symptom management is usually via the community teams and neurologists.	Comment noted. No change to the scope required.
		Would OTL-200 be offered for pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or also for MLD in adults? Yes, it should be offered to all these groups.	Comment noted. As discussed at the scoping workshop, the technology will be evaluated within its marketing authorisation.
		Would OTL-200 be offered to people with MLD and who have had stem cell transplant? Probably not, as the effect of the treatment on the transplant are unknown. There is the potential for inducing unwanted immune responses, for example. **How are the services for pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or adult type MLD organised in**	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		the NHS? Is it expected that OTL-200 would be delivered within the existing framework of services, or would new treatment centres be required? The existing LSD centres would be sufficient to provide the treatment and no new centres would be required. Referral to the tertiary LSD centres is made once the diagnosis is established, even if it is for a one-off opinion and the treatment can be offered if appropriate. Long term management of symptoms via the community teams and neurologists can continue.	Comment noted. No change to the scope required.
		Have all relevant comparators for OTL-200 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for MLD? How should best supportive care be defined? The comparators are appropriate. Currently only supportive care is considered established and HSCT is considered on a case by case basis through the national metabolic HSCT MDT meeting. Supportive care would include management of symptoms via the multidisciplinary team including neurology, neurodisability, metabolic, community paediatric and adult services, physiotherapy, speech and language therapy, CAMHS, psychology, pain management, surgery, nutritional support, educational support, palliative care. Common symptoms that need addressing include seizures, spasticity, dystonia, pain, behavioural and psychiatric disturbances (in late onset forms), unsafe swallow, excessive secretions, frequent chest infections, constipation.	Comment noted. As agreed at the scoping workshop, best supportive care and stem cell transplant are the relevant comparators for this evaluation.
		Are the outcomes listed appropriate? Are there other outcomes that should be considered? Yes, these are appropriate.	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The MPS Society	**How many people have pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or adult type MLD in England? For each subtype, how many new cases are diagnosed each year in England?** The incidence of pre symptomatic patients in England is likely to be low as most are diagnosed by being symptomatic. **How are the services for pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or adult type MLD organised in the NHS? Is it expected that OTL-200 would be delivered within the existing framework of services, or would new treatment centres be required?** It is anticipated that OTL-200 would be administered within the current specialised services framework	Comment noted. No change to the scope required. Comment noted. No change to the scope required.
	Orchard Therapeutics	***How many people have pre-symptomatic late infantile MLD, pre- or early-symptomatic juvenile MLD, or adult type MLD in England? For each subtype, how many new cases are diagnosed each year in England?*** There are no available studies presenting prevalence data for the UK. In a recent advisory board convened by Orchard Therapeutics, MLD clinical experts mentioned that incidence is estimated as 1-2 patients per annum. The incidence of MLD subtypes has been recorded in the UK (Stellitano 2016). The study shows an incidence of: • 0.51/100,000 live births for late infantile patients • 0.09/100,000 live births for early juvenile (EJ) • 0.08/100,000 live births for late juvenile (LJ) The study does not state the number of adults diagnosed each year.	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are people with MLD (including the 3 main subtypes) routinely tested for genetic mutations? How are MLD and its main subtypes identified and diagnosed in practice? Are there variations across the country regarding the identification and diagnosis of MLD and its main subtypes? In the absence of family history, the onset of symptoms is the trigger event that leads to diagnosis of MLD. MLD is suspected in individuals with the following: • Progressive neurologic dysfunction: Presenting signs may be behavioural or motor. Progression is determined both by medical history and by physical examination. Family history of neurological disease, time of onset of neurological symptoms, the presence of gait abnormalities, spasticity, decreased muscle stretch reflexes are also important considerations • Magnetic resonance imaging (MRI) evidence of disease-specific demyelination patterns: Diffuse symmetric abnormalities of periventricular myelin with hyper-intensities on T-weighted images. Initial posterior involvement is observed in most late-infantile cases with subcortical U-fibres and cerebellar white matter spared. As the disease progresses, MRI abnormalities become more pronounced in a rostral-to-caudal progression; cerebral atrophy develops. Anterior lesions may be more common initially in individuals with later onset If MLD is suspected, diagnosis is based upon combination of biochemical procedures and genetic analysis.	Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• ARSA activity: On clinical suspicion of MLD, ARSA enzyme activity is usually measured in isolated blood leukocytes or cultivated skin fibroblasts. The diagnosis of MLD is suggested by ARSA enzyme activity in leukocytes that is less than 10% of normal controls using the usual Baum type assay. • Urinary sulphatides: Sulphatides accumulate in kidney epithelial cells in MLD and eventually slough into the urine in amounts from 10- to 100-fold higher than controls as measured by thin layer chromatography, high-pressure liquid chromatography, and/or mass spectrometric techniques. Because urine production is highly variable, urinary sulphatide excretion is referenced on the basis of urinary excretion in 24 hours or to another urinary component such as creatinine. • Molecular analysis: Because low ARSA activity can occur in healthy individuals (pseudodeficiency [PD] mutation occurs at an estimated rate of 5-20%) the diagnosis of MLD can also be confirmed by molecular genetic analysis of the ARSA gene. This testing is used for confirmatory diagnostic testing to determine if low ARSA enzyme activity results from either of the following: o Homozygosity or compound heterozygosity for an ARSA-MLD variant(s). o A combination of known non-disease-causing alleles such as ARSA-PD homozygosity or compound heterozygosity for an ARSA-MLD and an ARSA-PD variant, which suggest the carrier state for MLD.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Would OTL-200 be offered for pre-symptomatic late infantile MLD, pre- or early-symptomatic juvenile MLD, or also for MLD in adults? OTL-200 proposed indication is for the treatment of MLD in patients from birth to before 17 years and in older patients for whom disease onset occurred before 17 years. Treatment with OTL-200 should be performed before the disease enters its rapidly progressive phase**.** [redacted] ***Would OTL-200 be offered to people with MLD and who have had stem cell transplant?*** [redacted]	Comment noted. The technology will be evaluated within its marketing authorisation. Comments noted. Information that is confidential cannot be added to the scope. No change to the scope. Comments noted. Information that is confidential cannot be

Section	Consultee/ Commentator	Comments [sic]	Action
		How are the services for pre-symptomatic late infantile MLD, pre- or early-symptomatic early juvenile MLD, or adult type MLD organised in the NHS? Is it expected that OTL-200 would be delivered within the existing framework of services, or would new treatment centres be required? Treatment with OTL-200 closely resembles the administration process used for HSCT. Stem and progenitor cells are harvested from the patient's bone marrow or collected from mobilised peripheral blood, and before infusion of the drug product the patient also receives busulfan conditioning. OTL-200 will be administered in qualified treatment centres by trained healthcare professionals with experience in HSCT. Physicians and healthcare professionals administrating OTL-200 will become qualified through trained on the product characteristics, product administration and management of related adverse events. Orchard Therapeutics believes that the therapy can be deliver within the existing framework and no new centres would be needed. ***Have all relevant comparators for OTL-200 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for MLD? How should best supportive care be defined?*** For relevant comparators and treatments considered to be established clinical practice in the NHS for MLD please see the 'Comparators' section. ***Are there any other subgroups of people in whom OTL-200 is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?***	added to the scope. No change to the scope. Comment noted. No change to the scope required. Comment noted. As agreed at the workshop, best supportive care and stem cell transplant are the relevant comparators for this evaluation.

Section	Consultee/ Commentator	Comments [sic]	Action
		OTL-200 should be assessed within its full marketing authorisation indication. There is no reason to believe that there are other subgroups in whom OTL-200 is expected to provide greater benefits or more value for money. ***NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf).*** Orchard Therapeutics welcomes and is in agreement with the intention of NICE to evaluate this technology through the HST programme. **References** 1 van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. Best Pract Res Clin Endocrinol Metab. 2015;29(2):261-73. 2 Bergner CG, van der Meer F, Winkler A, et al. Microglia damage precedes major myelin breakdown in X-linked adrenoleukodystrophy and metachromatic leukodystrophy. Glia. 2019;67(6):1196-209. 3 Gieselmann V, Krageloh-Mann I. Metachromatic leukodystrophy--an update. Neuropediatrics. 2010;41(1):1-6. 4 Kolodny. Metachromatic leukodystrophy and multiple sulfatase deficiency: sulfatide lipidosis. In: Scriver CR BA, Sly WS, Valle D, editor. The Metabolic and Molecular Bases of Inherited Disease. 7th ed. NY1995. p. 2693-740. 5 Von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. The metabolic & molecular bases of inherited disease2001. p. 3695-724.	Comment noted. No change to the scope required. Comment noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		6 Biffi A, Cesani M, Fumagalli F, et al. Metachromatic leukodystrophy - mutation analysis provides further evidence of genotype-phenotype correlation. Clin Genet. 2008a;74(4):349-57. 7 Elgün S, Kehrer C, Raabe C, et al. Influence of Age and Type of First Symptoms on Disease Progression in Metachromatic Leukodystrophy. 2019;50(S 02):GNP-PO42. 8 Mahmood A, Berry J, Wenger DA, et al. Metachromatic leukodystrophy: a case of triplets with the late infantile variant and a systematic review of the literature. J Child Neurol. 2010;25(5):572-80. 9 Heim P, Claussen M, Hoffmann B, et al. Leukodystrophy incidence in Germany. Am J Med Genet. 1997;71(4):475-8. 10 Hult M, Darin N, von Dobeln U, et al. Epidemiology of lysosomal storage diseases in Sweden. Acta Paediatr. 2014;103(12):1258-63. 11 Lugowska A, Poninska J, Krajewski P, et al. Population carrier rates of pathogenic ARSA gene mutations: is metachromatic leukodystrophy underdiagnosed? PLoS One. 2011;6(6):e20218. 12 Pinto R, Caseiro C, Lemos M, et al. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet. 2004;12(2):87-92. 13 Poorthuis BJ, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in The Netherlands. 1999;105(1-2):151-6. 14 Stellitano LA, Winstone AM, van der Knaap MS, et al. Leukodystrophies and genetic leukoencephalopathies in childhood: a national epidemiological study. Dev Med Child Neurol. 2016;58(7):680-9. 15 https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/metachromatic-leukodystrophy-late-infantile-form 16 MLD Support Association UK About MLD [online, accessed October 2019] 17 Gomez-Ospina N. Arylsulfatase A Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of	

Section	Consultee/ Commentator	Comments [sic]	Action
		Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1130/?report=classic. 2006. 18 Ługowska A, Berger J, Tylki-Szymańska A, et al. Molecular and phenotypic characteristics of metachromatic leukodystrophy patients from Poland. 2005;68(1):48-54. 19 Araya K, Sakai N, Mohri I, et al. Localized donor cells in brain of a Hunter disease patient after cord blood stem cell transplantation. Mol Genet Metab. 2009;98(3):255-63. 20 Biffi A, Capotondo A, Fasano S, et al. Gene therapy of metachromatic leukodystrophy reverses neurological damage and deficits in mice. J Clin Invest. 2006;116(11):3070-82. 21 Biffi A, De Palma M, Quattrini A, et al. Correction of metachromatic leukodystrophy in the mouse model by transplantation of genetically modified hematopoietic stem cells. J Clin Invest. 2004;113(8):1118-29. 22 Capotondo A, Milazzo R, Politi LS, et al. Brain conditioning is instrumental for successful microglia reconstitution following hematopoietic stem cell transplantation. Proc Natl Acad Sci U S A. 2012;109(37):15018-23. 23 Gabande-Rodriguez E, Perez-Canamas A, Soto-Huelin B, et al. Lipid-induced lysosomal damage after demyelination corrupts microglia protective function in lysosomal storage disorders. EMBO J. 2019;38(2). 24 Sevin C, Aubourg P, Cartier N. Enzyme, cell and gene-based therapies for metachromatic leukodystrophy. J Inherit Metab Dis. 2007;30(2):175-83. 25 Solders M, Martin DA, Andersson C, et al. Hematopoietic SCT: a useful treatment for late metachromatic leukodystrophy. Bone Marrow Transplant 2014;49(8):1046e51. 26 Meuleman N, Vanhaelen G, Tondreau T, et al. Reduced intensity conditioning haematopoietic stem cell transplantation with mesenchymal stromal cells infusion for the treatment of metachromatic leukodystrophy: a case report. Haematologica 2008;93(1):e11e3.	

Section	Consultee/ Commentator	Comments [sic]	Action
		27 Gomez-Ospina N. Arylsulfatase A Deficiency. 2006 May 30 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.	

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

None