

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Highly Specialised Technologies Evaluation**

**Lenti-D for treating cerebral adrenoleukodystrophy**

**Draft scope**

**Draft remit/evaluation objective**

To evaluate the benefits and costs of Lenti-D within its marketing authorisation for treating cerebral adrenoleukodystrophy (CALD) for national commissioning by NHS England.

**Background**

Adrenoleukodystrophy (ALD) is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids (VLCFAs) results in diffuse and multifocal demyelination (when myelin is damaged) of the nervous system and adrenocortical insufficiency. In ALD, the gene (ABCD1) responsible for the breakdown of fatty acids is faulty, causing damage to the adrenal glands, myelin, brain cells and the rest of the body<sup>1</sup>.

As the disorder is caused by a faulty gene from the X-chromosome it almost exclusively impacts upon males, as they only have one X-chromosome. Females can be affected, but the likelihood is much lower as the presence of another unaffected X-chromosome mitigates symptoms and damage. ALD affects around 1 in every 17,900 males worldwide<sup>2</sup>, or 1 in every 21,000 births<sup>2</sup>, although estimates vary.

Cerebral adrenoleukodystrophy (CALD) is the most common form of ALD (around 45% of cases)<sup>3</sup>, which usually affects male children and is characterised mainly by cerebral demyelination. Symptoms tend to present between the ages of 2 and 10<sup>4</sup>. When the myelin is damaged the nerves in the brain cannot work properly, and the person's functioning (such as reasoning, speech and mobility) are lost. ALD can be diagnosed after blood testing for high plasma concentrations of VLCFAs and additional blood tests may be done to confirm the ABCD1 gene mutation<sup>5,7</sup>. However, close monitoring is needed for the diagnosis of CALD as its early clinical symptoms are often misdiagnosed<sup>4</sup>. Progression of CALD is fast, symptoms worsen over the course of several months/years, leading to total dependency and eventually death<sup>4</sup>.

Current treatment options for children with CALD are limited but can include stem cell transplantation, using either umbilical cord stem cells or bone marrow stem cells<sup>5</sup>, and Lorenzo's oil. Stem cell transplant is considered in boys who have been diagnosed with the condition but in whom symptoms have not yet appeared. Better outcomes are associated with stem cell transplants from matched and related donors<sup>6</sup>. Lorenzo's oil is a combination of two fats extracted from olive oil and rapeseed oil which reduces the levels of VLCFAs<sup>8</sup> but does not address the underlying causes.

### The technology

Lenti-D (brand name unknown, Bluebird bio) is a viral vector which is used in gene therapy. Haematopoietic stem cells with the CD 34 marker are taken from the patient's bone marrow. The lenti-D vector is used to insert a healthy version of the disease-causing gene (ABCD1) into the stem cells which are then grown in culture. They are administered back to the body after myeloablative treatment (radio or chemotherapy). This gene addition aims to allow the production of functional adrenoleukodystrophy protein (ALDP), to potentially prevent further neurodegeneration. It is administered intravenously.

Lenti-D does not currently have a marketing authorisation in the UK for treating CALD. It has been studied in clinical trials in males aged under 18 years who have active CALD and do not have a willing 10/10 HLA-matched sibling donor.

<b>Intervention(s)</b>	Lenti-D
<b>Population(s)</b>	People aged under 18 years with cerebral ALD without a 10/10 HLA-matched sibling donor
<b>Comparators</b>	Established clinical management without Lenti-D
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• proportion alive without major functional disabilities (MFDs)</li> <li>• change in MFDs from baseline</li> <li>• proportion who undergo subsequent stem cell transplantation</li> <li>• proportion who experience acute, chronic or worsening graft versus host disease (GVHD)</li> <li>• overall survival</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life (for patients and carers).</li> </ul>
<b>Nature of the condition</b>	<ul style="list-style-type: none"> <li>• disease morbidity and patient clinical disability with current standard of care</li> <li>• impact of the disease on carer's quality of life</li> <li>• extent and nature of current treatment options</li> </ul>
<b>Clinical Effectiveness</b>	<ul style="list-style-type: none"> <li>• overall magnitude of health benefits to patients and, when relevant, carers</li> <li>• heterogeneity of health benefits within the</li> </ul>

	<p>population</p> <ul style="list-style-type: none"> <li>robustness of the current evidence and the contribution the guidance might make to strengthen it</li> </ul>
<b>Value for Money</b>	<ul style="list-style-type: none"> <li>cost effectiveness using incremental cost per quality-adjusted life year</li> <li>patient access schemes and other commercial agreements</li> <li>the nature and extent of the resources needed to enable the new technology to be used</li> </ul>
<b>Impact of the technology beyond direct health benefits</b>	<ul style="list-style-type: none"> <li>whether there are significant benefits other than health</li> <li>whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services</li> <li>the potential for long-term benefits to the NHS of research and innovation</li> <li>the impact of the technology on the overall delivery of the specialised service</li> <li>staffing and infrastructure requirements, including training and planning for expertise.</li> </ul>
<b>Other considerations</b>	<ul style="list-style-type: none"> <li>guidance will only be issued in accordance with the marketing authorisation.</li> <li>guidance will take into account any Managed Access Arrangements</li> </ul>
<b>Related NICE recommendations and NICE Pathways</b>	None
<b>Related National Policy</b>	<p>NHS England (2018), <a href="#">Manual for prescribed specialised services 2018/19</a> Chapter 100: Severe combined immunodeficiency and related disorders service (children) and Chapter 62: Highly specialist metabolic disorder services (adults and children)</p> <p>Department of Health and Social Care (2018) <a href="#">The UK Strategy for Rare Diseases. Second Progress Report from the UK Rare Diseases Policy Board</a></p> <p>NHS England (2017) <a href="#">Commissioning Medicines for Children in Specialised Services</a></p>

	<p>Department of Health (2016) <a href="#">The UK Strategy for Rare Diseases. Rare Diseases implementation plan for England</a></p> <p>NHS England (2018) <a href="#">National Programmes of Care and Clinical Reference Groups: E04. Paediatric Neurosciences</a></p> <p>NHS England (2013) <a href="#">2013/14 NHS standard contract for paediatric neurosciences- neurodisability</a>. Reference: E09/S/c</p> <p>Department of Health, The NHS Outcomes Framework 2016/17, (2016). <a href="https://www.gov.uk/government/publications/nhsoutcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhsoutcomes-framework-2016-to-2017</a></p>
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### Questions for consultation

How is CALD diagnosed in NHS practice?

Is CALD typically diagnosed before symptoms develop? Would Lenti-D be a treatment option for asymptomatic and/or symptomatic CALD?

Which treatments are considered to be established clinical practice in the NHS for people aged under 18 years with CALD?

Do these treatment options differ depending on the availability of a willing 10/10 HLA-matched sibling donor?

Are stem cell transplants considered as a treatment option for those with a less than 10/10 HLA-matched sibling, an unrelated matched donor or an unrelated mismatched donor? If so, are outcomes expected to vary with these options?

Are the outcomes listed appropriate? Are there any other important outcomes that should be included?

What services exist for the diagnosis and management of CALD in people aged under 18 years in the NHS? How many treatment centres in the NHS would provide treatment with Lenti-D?

What is the size of the population that would be eligible for treatment with Lenti-D in England?

Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Lenti-D will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

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>.)

### References

1. ALEX, the leukodystrophy charity. <https://www.alextlc.org/what-is-a-leukodystrophy/the-different-leukodystrophies/adrenoleukodystrophy-ald/> (accessed October 2020)
2. Bezman L, Moser AB, Raymond GV et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. *Ann Neurol.* 2001 Apr;49(4):512-7.
3. Stop ALD Foundation. <http://www.stopald.org/what-is-ald/> (accessed October 2020)

4. Engelen M, Kemp S, Visser M et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012; 7: 51.
5. Great Ormond Street Hospital for Children  
<https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/adrenoleukodystrophy> (accessed October 2020)
6. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2019 Mar;25(3):538-548.
7. ALD Connect. <http://aldconnect.org/education-and-support/what-is-ald> (accessed October 2020)
8. Adrenoleukodystrophy info  
<https://adrenoleukodystrophy.info/treatment-options/lorenzos-oil> (accessed October 2020)