NICE National Institute for Health and Care Excellence

HST routing criteria (refined April 2025)

Leriglitazone for treating cerebral adrenoleukodystrophy in people 2 years and over [ID3903]

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Introduction

1. The NICE HST routing assessment checklist highlights when a technology meets or does not meet the criteria for routing it to the HST Programme. All 4 criteria need to be met for a technology to be routed to HST.

2. Marketing Authorisation (MA) wording (April 2026, company anticipated): [redacted]

3. **Prioritisation Board routing discussion** 13/05/2026

4. **Description of the HST Programme's vision**

Criterion 1 - The rarer a disease is, the more challenging it is to do research and generate an evidence base that is robust enough to bring an effective technology to market. The HST Programme's vision aims to encourage research when it is most challenging.

Not all ultra-rare diseases are debilitating. The vision focuses on ultra-rare diseases that cause ongoing debilitating symptoms and have an exceptional burden on the people with them, and on their carers and families. This is to justify prioritising access to HST technologies over overall population health.

Criteria	**Descriptions of how the criteria are met or not met through assessing the definitions**
Criterion 1 **The disease is ultra-rare, that is,** • **1A: it is defined as having a point prevalence of 1:50,000 or less in England (NICE strategic principles for rare disease).** **....and debilitating, that is,**	These definitions have been developed to help define what an ultra-rare disease is, and the debilitating nature of the disease. Relevant information should be collected during scoping by NICE (from the company, and other research or academic sources) to explain how each definition is considered by the NICE prioritisation board. • 1A of routing criterion 1 is about defining the ultra-rare 'disease', not about the symptoms associated with the ultra-rare disease (regardless of whether the symptom or set of symptoms are the dominating feature). 1B of routing criterion 1 is about the characteristics of the ultra-rare disease. • 'Disease' refers to a condition for which a diagnosis can be made using the International Classification of Diseases (ICD11) developed by the World Health Organization (WHO) as a guiding tool. Diagnosis is based on a unique set of signs and symptoms (characteristics) identified using:

• **1B: it is lifelong after diagnosis with current treatment, and has an exceptional negative impact and burden on people with the ultra-rare disease, and their carers and families.**	○ clinical examination ○ patient history ○ imaging or laboratory tests that are, or can be made, available in the NHS in England. • 'Disease' does not refer to subgroups based on age, sex, severity, or genetic subtype. These will only be considered if they are clinically meaningful. • 'Point prevalence' refers to the point prevalence of the 'disease' in England. It counts the number of people with a diagnosis of the disease thought to be alive in England (numerator) on a given index date compared with the total population of England (denominator) at that time (NHS England).
	1B of routing criterion 1 definitions: • 'Lifelong' indicates that the disease needs ongoing clinical management, supportive care, or both. • 'Exceptional negative impact' refers to shortened length of life or severely impaired quality of life. The precise assessment of this will require an element of subjective judgement.
	Has this criterion been met? Yes ☒ No ☐
	Notes and rationales: **Criterion 1A:** **Classification of the disease** • Adrenoleukodystrophy (ALD) is a rare X-linked metabolic disorder.[1–3] It is caused by genetic mutations in the ABCD1 gene that are inhered recessively.

	• X-linked adrenoleukodystrophy (or ALD) is a classified disorder under International Classification of Diseases ICD-11: 5C57.1 (Disorders of peroxisomal alpha-, beta- or omega-oxidation); 8A44.1 (Adrenoleukodystrophy). There is not a specific ICD-11 code for cerebral adrenoleukodystrophy. • Clinical presentation of ALD has 3 main phenotypes: cerebral ALD (CALD), adrenomyeloneuropathy (AMN) and adrenal insufficiency. CALD and AMN can co-exist with adrenal insufficiency, and AMN can progress into CALD. • The prognosis and management of ALD varies by subtype (CALD is the most severe). • As described in ICD-11, the 'disease' is classified as ALD. **Prevalence** Population-based studies in Europe suggest a point prevalence for ALD of 0.4 to 0.7 in 50,000, based on clinical presentation combined with genetic analysis. • The point prevalence of ALD in Norway on 1 July 2011 was 0.4 per 50,000 inhabitants, in a population based, cross-sectional prevalence study, supplemented by a retrospective study of deceased subjects.[4] • The point prevalence of ALD in Denmark on 1 December 2024 was 0.71 per 50,000 in a single cohort study based on patients' medical records. The study authors noted that while the birth incidence aligns with some other natural history studies, it remains lower than in countries with universal newborn screening.[5] • US studies using genetic screening alone suggest a higher prevalence for ALD: 2.9 in 50,000 (1 in 17,000) based on extended family screening[6], and 3.4 to 4.8 in 50,000 (1 in 10,500 to 1 in 14,700) in newborn screening programmes[7-10]. • However some of the people identified via genetic screening alone may not develop symptomatic ALD, or may only develop a very mild form of the disease. This is particularly the case for females, who have a second, healthy copy of the ABCD1 gene. Also, many different mutations of the ABCD1 gene have been identified in ALD and there is no indication from genetic analysis what phenotype(s) of ALD will occur or when symptoms would begin.

	• So the prevalence estimates for this disease should include clinical presentation, and not be based solely on genetic testing. Taking this into account, studies indicate that fewer than 1 in 50,000 England in the UK are affected by ALD. **Criterion 1B:** Most people with ALD have CALD or AMN, which differ in clinical course. CALD typically has an exceptional negative impact and a very short life expectancy. AMN is a life-long condition associated with progressive spinal cord damage and associated disability and burden; AMN can progress to CALD. • CALD is the most common form of ALD (~45%): Progression of CALD is fast, leading to complete dependency with people losing ability to see, speak, swallow or be mobile, and having incontinence, cognitive decline and premature death.[11] Estimated survival is ~3.5 years from onset of CALD, although can be longer in a vegetive state. Once cerebral involvement in ALD is identified, the prognosis and management of the condition changes significantly. CALD usually presents in childhood, at around 2.5 to 10 years. • Around 40-45% of ALD is AMN: It usually presents in male adults aged in mid 20s. AMN is associated with neurological problems that mainly the affect spinal cord. These include progressive paraparesis, incontinence, impotence and adrenal insufficiency. Progression of AMN is slow, over many decades, with a close to normal life expectancy (if no cerebral involvement). But around 20% of AMN progresses to CALD, which has a much more rapidly progressing course.

5. Description of the HST Programme's vision

Criterion 2 - This criterion is designed to uphold the HST Programme's vision to encourage innovation and research into ultra-rare and debilitating diseases for which there is poor service provision within the NHS (for example, delay in diagnosis, no treatment options beyond supportive care). Without these incentives from the HST Programme, the technology may not be available either after launch, or during development or testing of the technology in England. The availability of the innovation can also reshape NHS services and advance awareness.

Criteria	Descriptions of how the criteria are met or not met through assessing the definitions

Criterion 2
The technology is an innovation for the ultra-rare disease.
	These definitions have been developed to help define an innovative technology. Information about the technology should be collected by NICE from relevant sources (for example, the Medicines and Healthcare products Regulator Agency [MHRA], ongoing trials, registries) to explain how each definition is considered.
	
	• 'Innovation' refers to a technology or medicine such as an advanced therapy medicinal product (ATMP), a new chemical or biological entity, or a novel drug device combination that brings additional health gains to people with the ultra-rare disease (compared with existing treatment or best supportive care).
	• To ensure the technology is an innovation for the ultra-rare disease:
	  ○ the technology should not be a repurposed technology
	  ○ the indication for the technology should not be a significant extension of an indication from another population or disease.
	
	• A repurposed technology means new uses for medicines that are outside the scope of the existing licence for the medicine. This typically involves taking an existing medicine that already has a marketing authorisation or licence for human use for a particular condition and then using it to treat another condition. This can also include generic treatments or treatments that have had marketing authorisation withdrawn and the developer is seeking a new indication.

	Has this criterion been met? Yes ☒ No ☐
	Notes and rationales: • There are no drug treatments available for use in NHS practice that stop or reverse the underlying disease process. Standard care is HSCT for boys and men with CALD (if performed early). • Leriglitazone, is a new chemical entity – it is an active metabolite of the diabetic medicine pioglitazone. Leriglitazone is a novel selective peroxisome proliferator-activated receptor gamma agonist.[12] It regulates expression of key genes involved in mitochondria synthesis which can help counteract the neuroinflammatory and neurodegenerative processes in ALD that damage nerve cells and the myelin surrounding them in the brain and spinal cord. • Leriglitazone is an oral treatment that can cross the blood–brain barrier where it is anticipated it could protect and repair neurons and myelin that are damaged by the toxic build-up of very long-chain fatty acids (VLCFAs) improving brain and motor function. Non-clinical and preliminary clinical data show that leriglitazone distributes to the central nervous system (CNS) and achieves local concentrations sufficient for target engagement needed for interfering with ALD progression. • The company reports that leriglitazone has completed a phase 2/3 clinical study in adult patients with X-ALD (ADVANCE) in the EU and US showing a significant reduction of cerebral lesion progression and a reduction of incidence of progressive CALD. Additionally, a separate study in paediatric patients with CALD (NEXUS) is currently ongoing in EU and after 24 weeks of treatment, all evaluable patients in NEXUS were clinically stable and radiologically demonstrated disease arrest or lesion growth stabilization.[13] • Leriglitazone is currently in less advanced clinical development for other orphan CNS disorders, including with a clinical trial completed in Friedreich's Ataxia.[13]

6. Description of the HST Programme's vision

Criterion 3 - This criterion is designed to establish the acceptability of the technology as an effective use of NHS resources, considering the significantly higher ICER threshold. So, the eligible population needs to be small. This is to strike a balance between the desirability of supporting access to treatments for ultra-rare diseases and the inevitable reduction in overall health gain across the NHS because of a higher ICER threshold. A small subpopulation within a population with a common disease would not be suitable for the HST Programme.

Criteria	**Descriptions of how the criteria are met or not met through assessing the definitions**

Criterion 3
No more than 300 people in England are eligible for the technology in its licensed indication, and the technology is not an individualised medicine
	These definitions have been developed to help define what kind of licensed indication is suitable for a technology to be considered for routing to the HST Programme, and to help explain what an individualised medicine is. Relevant information about the licensed indication of the technology should be collected by NICE to explain how each definition is considered.
	
	• 'Eligible' refers to everyone who could have the technology under its marketing authorisation (obtained or in the process of being obtained) in England.
	
	• The 'technology' should only be developed for the ultra-rare disease, so the eligible population is small. The technology:
	
	  ○ has to be the first licensed treatment indicated for the ultra-rare disease under consideration
	  ○ should not be an extension of an indication from another:
	  • related population or disease, or
	  • subgroup of people with the same ultra-rare disease under consideration

	○ is unlikely to be suitable for other subgroups of the population with the ultra-rare disease in the future who are outside of its first indication. • 'Individualised medicine' refers to a medicine that is developed based on a person's unique genetic profile (n of 1), or on the genetic profile of monozygotic twins or triplets.
	Has this criterion been met? Yes ☒ No ☐
	Notes and rationales: Data on known ALD cases in England suggests substantially fewer than 300 people (around 47 to 53 boys) in England have CALD and would be eligible for leriglitazone: • During consultation on a previous version of the draft scope in 2023, Alex, The Leukodystrophy Charity, a consultee submitted numbers from their database of known males living in the UK with ALD at that time. Of the 197 known males with ALD included in the database, 47 were children with CALD; a further 6 boys/men had arrested CALD, so were potentially eligible for leriglitazone. Of 197 males with CALD, ~25% had been treated with HSCT, including adults. • Commenting on the 2026 draft scope, Alex, The Leukodystrophy Charity noted that 106 people (boys and men) with CALD in the UK could be eligible for leriglitazone. • CALD is managed through 4 specialist metabolic or inherited white matter disorder services in the NHS: ○ A commentator from Great Ormond Street Hospital for the 2023 scoping consultation noted their centre see ~1-2 new boys with CALD per year who might be eligible for leriglitazone. ○ An expert from NHS England for the 2026 scoping consultation estimated that around 5 to 7 new cases of CALD in boys are seen each year.

	• The company took a different approach, which predicted the number male births diagnosed with CALD and alive in England per year. This calculation also predicted the eligible population for leriglitazone would be substantially below 300 boys (the exact figure is confidential so cannot be reported here).

7. Description of the HST Programme's vision

Criterion 4 - This criterion is designed to address the lack of effective treatment and access to NHS services for some ultra-rare diseases. To justify prioritising treatment access for ultra-rare diseases over overall population health, the technology under consideration should be anticipated to provide substantial health benefits to people with the disease over existing clinical management and supportive care.

Criteria	Descriptions of how the criteria are met or not met through assessing the definitions

Criterion 4
The technology is likely to offer substantial additional benefit for people with the ultra-rare disease over existing established clinical management, and the existing established clinical management is considered inadequate.
	These definitions have been developed to help define what is substantial additional benefit, and to help to explain the meaning of no other treatment options. Relevant information should be collected by NICE to explain how each definition is considered.
	
	• 'Substantial additional benefit' means that the technology is likely to:
	  ○ significantly redress the reduced length of life, or
	  ○ is likely to demonstrate substantial improvements in the severely impaired quality of life attributable to the ultra-rare disease, as exemplified by research data on clinically relevant measures, for example, patient-reported outcome measures (PROMs).
	
	• 'The technology' means that:
	  ○ if the technology is a disease-modifying treatment (including curative treatment), there is no other disease-modifying treatment available in the NHS in England for the same ultra-rare disease at the time of the routing decision, or

	○ if the technology treats a symptom or set of symptoms unique to the ultra-rare disease, there is no other treatment available in the NHS in England for the same symptom for which the technology is indicated at the time of the routing decision.
	Has this criterion been met? Yes ☒ No ☐

	Notes and rationales:
	
	Leriglitazone is the first disease-modifying treatment for CALD. It would provide a treatment option to people with early-stage CALD where HSCT is unsuitable or unavailable.
	
	• Allogenic stem cell transplantation is the gold standard and only current treatment can stop CALD progressing.[14] It is available in the NHS for paediatric and adult male patients with early-stage CALD but has strict eligibility criteria.
	• Registry data suggests that the majority of people with CALD do not have HSCT. Leriglitazone is expected to provide an alternative option for early-stage CALD where HSCT isn't available or suitable.
	• Reasons for HSCT being unsuitable of unavailable for early-stage CALD include:
	  • Absence of active brain lesions
	  • Lack of donor availability
	  • Lack of access to specialist treatment centre
	  • Comorbidities or infection risk which precludes safe conditioning
	• HSCT is an aggressive treatment option associated with complications such as graft versus host disease and graft failure, and long term side effects such as infertility and increased risk of cancer. Leriglitazone is a non-invasive oral treatment. It removes the burden of hospital stays, travel, time off etc. when compared to HSCT.

	• A commentator on the scope noted that the potential use of leriglitazone to stabilise patients prior to and during HSCT is of significant benefit and should be considered because CALD deterioration can continue for several months until the transplant stabilises the patient's condition. • For people not eligible for transplant or where it would not provide benefit, established clinical management is supportive care.[3]

Routing decision	**Overall routing decision:** HST☒ STA☐ **Other comments:**

References

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