NICE National Institute for Health and Care Excellence

HST routing criteria (refined April 2025)

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. **Proposed** Marketing Authorisation (MA) wording: [redacted]

3. **Prioritisation Board routing discussion** 16/06/2025

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 and debilitating, 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).**
 	
• **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.**
	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:
	  ○ 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 or not met? Yes ☒ No ☐
	1A notes and rationales: **<u>TK2D diagnosis if often based on genetic testing</u>** • Thymidine kinase 2 deficiency (TK2D) is listed under the disorders of pyrimidine metabolism in the ICD-11 – 5C55.1. • TK2D is diagnosed based on genetic testing. This can be done by single-gene testing, multiple gene panels, and comprehensive genomic testing. Scoping stakeholder comments: • *Company:* TK2D is diagnosed based on a detailed patient history, clinical examination, laboratory and genetic tests. The gold standard for confirming TK2D is based on genetic testing which may reveal pathologic variants in the nuclear TK2 gene. Genetic testing in the UK includes whole genome/exome sequencing and broad multi-gene panels. • *The Lily Foundation and Metabolic Support UK*: there is a standard testing pipeline established within the NHS to test for known genes responsible for causing mitochondrial diseases including TK2D. • *Genetic alliance:* a genetically confirmed TK2 mutation would be required, as per the trial, to avoid misdiagnosis and ensure correct targeting. **<u>The prevalence of TK2D in England is less than 1 per 50,000</u>**

	• A Prevalence Estimation of Thymidine Kinase 2 Deficiency: An Ultra-Rare Autosomal Recessive Mitochondrial Disease study estimates a worldwide prevalence of **1.64 in 1,000,000 people.**
	• Pharmascan UK patient population range: less than 1 per 50,000. The number of people in England with TK2D not reported in the literature.
	• Horizon scanning briefing note: The company has identified [redacted] living individuals with a confirmed TK2D diagnosis in the UK.
	
	Scoping stakeholder comments:
	• *Company:* while TK2D is still very rare, the "true" prevalence and fatality rates of TK2D may differ from estimates, as reported patients do not include those who are undiagnosed or misdiagnosed.
	
	1B criterion notes and rationales:
	
	From the onset of symptoms, people with TK2D will likely require lifelong support
	
	• TK2D is caused by a mutation in the TK2 gene. It is inherited in an autosomal recessive manner (inherit 2 copies of the mutated gene, one from each parent).
	• From the onset of symptoms, people with TK2D are likely to require lifelong support to manage their symptoms. The onset of symptoms can vary from birth to adulthood.
	• TK2D is split into 3 subtypes depending on the age of symptom onset:
	  ○ Infantile onset TK2D - the first symptom is before age 1 year.
	  ○ Childhood onset TK2D - the first symptom is between age 1 and 12 years.
	  ○ Late onset TK2D - the first symptom is after age 12 years.
	  ▪ The age of symptom onset in this subgroup is varied, with reports between age 13 and 72 years. Some literature has also reported people remaining asymptomatic until after age 40.

	TK2D has an exceptional negative impact on quality and length of life, particularly for those whose symptoms start aged 12 years and under. This accounts for most of the TK2D population • The impact of TK2D on the length and quality of life depends on the age of symptom onset. The subtype of TK2D affects the type, severity and progression of symptoms of TK2D. *Proportion of people with each subtype:* • Retrospective natural history study: 80% have symptom onset aged 12 years and under • Clinical and Genetic Analysis of Patients with TK2 Deficiency (study of people from Spain): 40% had symptoms aged 12 years and under. 26% of those with late onset remained asymptomatic until their 5th decade. Findings suggest a potential underdiagnosis of adult patients with this disorder. Scoping stakeholder comments: • *Company*: 77.4% with genetically confirmed TK2D had an age of symptom onset of 12 years and under. Two reviews found that approximately 85% of people with TK2D had an age of onset of 12 years and under • *The Lily Foundation and Metabolic Support UK*: publications suggest a 40/40/20 split among the severity subtypes, but we also note that misdiagnosis is more common among individuals with late-onset, which means there will be some uncertainty on the proportions estimated. ○ There are approximately 10-20 patients living with TK2d in England, of which approximately 2/3rds were symptomatic aged 12 years or under. • *Genetic Alliance*: worldwide data suggests an approximate 40:40:20 split. In principle all genetically confirmed, symptomatic patients would be eligible for treatment, although clinicians may fine-tune criteria based on symptom severity. *Survival* • Retrospective natural history study reports the median survival post-onset for each subtype of TK2D:

	○ Infantile onset (n=39): 1 year (CI 0.58-2.33) ○ Childhood onset (n=37): not estimated, but infer > 13 years (40th percentile value) ○ Late onset (n=14): 23 years (CI cannot be calculated). *Quality of life* • Patients' lived experience of thymidine kinase 2 deficiency (TK2d): results from the Assessment of TK2d Patient Perspectives (ATP) study (n=32) ○ Most frequent symptom: myopathy (100%), neurological (91%) and psychological (78%). ○ Most frequently reported impacts: walking /eating/toileting (81%), breathing (78%), development (delayed/loss of ability, 63%), feelings of isolation (53%). ○ Extreme HRQoL impact: walking (55%), breathing (28%), eating/swallowing difficulties (26%) ○ 78% needed home modifications and support with daily activities, 13% need full-time medical support. • The impact of TK2 deficiency syndrome and its treatment by nucleoside therapy on quality of life (n=25) ○ Physical domains most affected by TK2D: mobility (84%), fatigue (60%), respiratory function (56%), and hospitalizations (55%). ○ Psychosocial domains most affected: impact on family members (39%), mood (36%), and social life (28%). Quality of life impact by subtype - Retrospective natural history study • Infantile onset TK2D: most severe form ○ Many children are never able to walk or become wheelchair bound by age 4 (94%) and requiring breathing support (89%). • Childhood onset TK2D: less severe but symptoms still progress quickly. ○ The majority children need a wheelchair by age 10 (63%) and eventually require ventilator support (55%). • Late onset TK2D: least severe subtype, symptoms worsen gradually overtime

	○ Most people do not completely lose the ability to walk (0% became wheelchair bound). Breathing support may be required overtime (44%). Scoping stakeholder comments: • *The Lily Foundation and Metabolic Support UK*: Despite varying rates of progression, we believe that the impact on quality of life is substantial across all subtypes, as patients experience a gradual loss of skills and independence leading to an increased reliance on others and medical equipment. • *Company:* TK2D severely compromises patient quality of life, as well as the quality of life of patients' families. It inhibits their ability to participate in normal activities as compared to peers, including loss of functional independence with activities of daily living. Most patients require caregiver support. ○ Age of symptom onset is the best available predictor of disease severity and rate of progression. ○ People with symptom onset aged 12 years and under: ➢ Median post symptom onset survival of 2.6 years and median age at death of 4 years ○ People with symptom onset aged 13 years and over ➢ May live for several decades before symptom onset and may live for decades after symptom onset (median age at death is 67 years, with median post-symptom onset survival of 24 years). The prioritisation board noted that each subtype was associated with a different level of severity, with those experiencing symptoms earlier in life presenting with a more severe condition. In all subtypes, respiratory failure caused by respiratory muscle weakness is the most common cause of death. The board considered that people with a symptom onset aged 12 years and under (includes subtypes infantile onset and childhood onset) were significantly impacted by TK2D and this likely made up the majority of the diagnosed population. **Prioritisation board conclusion: criteria 1 is met.**

- **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 or not met? Yes ☒ No ☐
	Notes and rationales: **<u>Doxecitine and doxribtimine is an innovative technology designed to treat TK2D</u>** • Horizon scanning document – Doxecitine and doxribtimine is listed as a new active substance. • It does not have an indication/proposed indication for any other populations. • NIHR horizon scanning – targets the underlying pathophysiology of TK2D by restoring mitochondrial DNA replication fidelity. • There are currently no approved pharmacological treatment options for TK2D. Current treatment options are only supportive. **Prioritisation board conclusion: criteria 2 is met**

- **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 or not met? Yes ☒ No ☐
	Notes and rationales:

	The eligible population for doxecitine and doxribtimine is likely to be less than 300 people
	
	• [redacted] (Horizon scanning briefing note).
	• Proposed licensed indication: [redacted]
	
	Proportion of people with each subtype of TK2D varies in the literature, but reports suggest between 40% and 80% of people could have symptoms aged 12 and under [redacted]
	Scoping stakeholder comments:
	• *Company*: considerably less than 100 people with TK2d in England will be eligible for treatment.
	  ○ Given high rates of mortality, diagnostic delay and misdiagnoses, the number of people offered doxecitine and doxribtimine will be lower than the estimated prevalence.
	• *Genetic Alliance*: estimate fewer than 100 people in England.
	• *The Lily Foundation and Metabolic Support UK*: there are approximate 10-20 people living with TK2D in England, of which approximately 2/3rds were symptomatic aged 12 and under.
	
	Doxecitine and doxribtimine is the first TK2D treatment and may be suitable for another subgroup of TK2D. The population would remain below 300 people.
	
	• Doxecitine and doxribtimine is a new active substance and would be the first treatment for people with TK2D [redacted]
	• Doxecitine and doxribtimine is likely to be suitable for a subgroup of the TK2D population in future who are outside of its first indication – [redacted].
	  ○ It is also caused by a mutation to the TK2D gene but presents differently to the proposed licensed population in terms of the type, severity, progression and age of onset of symptoms.

	[redacted]The company trials tested doxecitine and doxribtimine on the entire population. Recent posters presented at the Muscular Dystrophy Association conference suggest that there is also [redacted] ○ [redacted], the expected eligible population would still be less than 300 people. Scoping stakeholder comments: • *Company*: No other indications for doxecitine and doxribtimine exist or are planned. [redacted] • *The Lily Foundation and Metabolic Support UK*: every patient should have access to treatment, our view is that making this treatment available to only a subset of individuals would lead to substantial inequalities among the TK2D community. **Individualised medicine – not an individualised medicine** • Horizon scanning briefing note: Doxecitine and doxribtimine is a fixed dose combination therapy that targets the underlying pathophysiology of TK2d by restoring mitochondrial DNA (mtDNA) replication fidelity. Doxecitine and doxribtimine consists of a combination of deoxynucleosides (the building blocks of mtDNA) given orally. Scoping stakeholder comments: • *Company*: Doxecitine and doxribtimine is not an individualised medicine. ○ Doxecitine and doxribtimine are unmodified pyrimidine nucleosides that are subject to complex metabolic and regulation pathways including additional pathways, such as non-

	mitochondrial ribonucleic acid and amino acid synthesis or nuclear deoxyribonucleic acid (DNA) replication. **Prioritisation board conclusion: criteria 3 is met**

- **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 or not met? Yes ☒ No ☐
	Notes and rationales: **<u>Doxecitine and doxribtimine offers substantial clinical benefit for people with TK2D, in particular for people with symptom onset aged 12 years and under</u>** Posters presented at Muscular Dystrophy Association (MDA) Clinical and Scientific Conference (16-19 March 2025) suggests doxecitine–doxribtimine offers substantial additional benefit to people with TK2D: *People with symptom onset aged 12 years and under:* • Doxecitine and doxribtimine decreases mortality and increases survival time of people with TK2D with symptom-onset age 12 years and under. It reduced risk of death by 92–94% (hazard ratio=0.06–0.08; p<0.0001) and 87–95% (hazard ratio=0.05–0.13; p<0.0001) in the time from symptom onset and starting treatment, respectively. • Doxecitine and doxribtimine improves functional outcomes including retaining/regaining motor milestones and stabilising ventilatory and feeding support use for people with TK2D with symptom-onset aged 12 years and under 75.0% (30/40) regained at least one previously lost motor milestone, with 22.5% (9/40) regaining four or more motor milestones. Ventilatory support dependency decreased, with 16.1% (5/31) of patients reducing usage time and 16.1% (5/31) discontinuing ventilatory support altogether after treatment.

	People with symptom onset aged 13 years and over: • Doxecitine and doxribtimine stabilises disease progression for people withTK2D with symptom onset age 13 years and over. As there is no alternative treatment, these benefits could be substantial, however, the size of the benefits appears smaller than for the population with symptom onset aged 12 years and under. Stakeholder consultation comments: • *Company:* [redacted] **Established clinical management for TK2D is inadequate. It only manages the symptoms and does not treat the underlying condition** • There are currently no approved pharmacological treatment options for TK2D. Current treatment options are only supportive. • Supportive care for people with TK2D can include respiratory support, feeding tubes, wheelchairs, physical therapy and working with a range of healthcare professionals such as neurologists, pulmonologists, geneticists, metabolic specialist and dietitians. Scoping stakeholder comments: • *The Lily Foundation and Metabolic Support UK:* established clinical management consists of supportive care only, that only manages the symptoms of TK2D rather than treating the condition. • *Company*: Best supportive care is inadequate and does not address the underlying disease. **There is no other disease-modifying treatment available to treat TK2D at the time of the routing decision**

	• Doxecitine and doxribtimine targets the underlying pathophysiology of TK2D by restoring mitochondrial DNA (mtDNA) replication fidelity (Horizon scanning document). • There are no approved pharmacological treatment options for TK2D. Current treatment options are only supportive. • Disease areas with similar symptoms (muscle weakness) include SMA and Pompe which have NICE-approved therapies. However, treatments would not be used to treat TK2D as they target the underlying cause of the condition which differs to TK2D. Scoping stakeholder comments: • *Company:* Doxecitine and doxribtimine represents a new class of treatment that can address unmet medical need in TK2D. **Prioritisation board conclusion: criteria 4 is met.**

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