National Institute for Health and Care Excellence

Health Technology Evaluation

Doxecitine–doxribtimine for treating thymidine kinase 2 deficiency in people of any age ID6484
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	UCB Pharma	This appraisal is not appropriate for a Single Technology Appraisal. As displayed on the NICE website after prioritisation in September 2024, a Highly Specialised Technology (HST) evaluation is appropriate. Doxecitine and doxribtimine fulfil all the criteria for a HST evaluation and should be evaluated by that committee using HST evaluation methods. In brief: • TK2d is an ultra-rare severe condition with high levels of mortality and morbidity that adversely affects people with the disease, carers, and their families.1–4, 9–12 • There are no approved medicinal treatments for TK2d and the current standard of care does not address the underlying disease or provide sufficient efficacy. • Doxecitine and doxribtimine is the first medicinal treatment for TK2d, is only pursuing a licence in TK2d, is not an individualised medicine, and is not a repurposed medicine.	Thank you for your comment. The routing of this topic was discussed in the prioritisation board meeting, and it was considered that this topic would be evaluated as a highly specialised technology.

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		• Doxecitine and doxribtimine has shown substantial clinical effectiveness, reducing both mortality and morbidity, and reversing functional loss in many people with TK2d.6,13 The blank HST company form supplied in response to this consultation provides full information on how doxecitine and doxribtimine for TK2d fulfil the HST criteria.	
	Salford Royal Hospital NCA	This is appropriate.	Thank you for your comment. Comment noted. No action required.
	The Lily Foundation and Metabolic Support UK	Based on the ultra-rarity and debilitating impact of TK2d, as well as the innovative, first-in-class nature of doxecitine–doxribtimine, we believe that it is appropriate for this technology to be routed through the highly specialised technology (HST) route as it meets all of the required criteria to be considered via this route. HST criteria 1 is met, as detailed in the background of the scope: the disorder is ultra-rare (1.64 in 1,000,000 people) and has debilitating, life-limiting impacts across all its severities. This also means HST criteria 3 is met, as less than 300 people in England are expected to be eligible for doxecitine–doxribtimine. We understand that approximately 10-20 people with TK2D have been diagnosed in England; further confirming the low prevalence of this disease. These statistics reflect our own experiences; as the largest mitochondrial disease patient organisation in the UK, we are in contact with a very small number of families who have ever received a diagnosis of TK2d for themselves or a loved one. Despite the small numbers, we also witness the particularly devastating impact that this condition has on those affected;	Thank you for your comment. The routing of this topic was discussed in the prioritisation board meeting, and it was considered that this topic would be evaluated as a highly specialised technology.

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		particularly in the infant population where the presentation is severe and prognosis is particularly poor, characterised by death in infancy. HST criteria 2 is met as doxecitine–doxribtimine is a novel drug, which has shown substantial health gains to the TK2d community in its trials. To our knowledge, doxecitine–doxribtimine is not and has not been tested in any other populations and is a specific treatment developed for people with TK2d. We believe that this product is truly innovative and disease-modifying because there are currently no available treatments for TK2d or any other form of mitochondrial disease available on the NHS in England. HST criteria 4 is met considering that the current treatment for TK2d is best supportive care. No disease-modifying treatments currently exist for TK2d, resulting in a substantial unmet need for this community. As described, current clinical care comprises of symptom management and use of assistive equipment such as mechanical ventilatory support, feeding assistance and support with moving including use of electric wheelchairs and other assistive equipment. This invasive management places a significant burden on caregivers, whilst severely impacting upon the quality of life of the person directly affected as well as on the wider family. Finally, we welcome the news that doxecitine–doxribtimine has been recently granted a PIMs designation by the MHRA (https://firstwordpharma.com/story/5957378). This decision further supports HST routing as it recognises TK2d as a life-threatening condition, with a substantial unmet medical need, which could be addressed by this innovative treatment.	

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		Gaining a PIMs designation also demonstrates that doxectine-doxribtimine has a positive risk-benefit profile, meaning that it is expected that the potential adverse effects of treatment are likely to be outweighed by the benefits of treatment.	
	Genetic Alliance	Genetic Alliance UK welcomes the opportunity from NICE to comment on the draft scope for doxecitine–doxribtimine (DoxTM) for thymidine kinase 2 deficiency (TK2D). When drafting our comments, we reached out to two of the stakeholders on the draft list that are members of Genetic Alliance UK to discuss this consultation (The Lily Foundation and Metabolic Support UK). We also reached out to Muscular Dystrophy UK (see the stakeholder box for context). On review of the draft scope, we suggest that routing DoxTM via the HST pathway is more appropriate for the following reasons: The HST pathway is intended for very rare, life-limiting conditions, as in the case of TK2D, which has an estimated prevalence of ~1.64/million people (criterion 1), and modelling suggests that far fewer than 300 people are expected to be eligible for the therapy in England (criterion 2). To our knowledge, the current treatment for TK2D is best supportive care only (criterion 4), so the context of this technology, an orally administered nucleoside therapy for an ultra-rare autosomal recessive mitochondrial disorder, is a first-in-kind treatment that could address the unmet need of people living with TK2D (criterion 3). We believe this therapy is truly innovative; we are not aware of any treatments for other forms of mitochondrial disease available on the NHS. Routing of DoxTM via the HST pathway would acknowledge that there is a small population that would be eligible for this therapy and allow more	Thank you for your comment. The routing of this topic was discussed in the prioritisation board meeting, and it was considered that this topic would be evaluated as a highly specialised technology.

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		flexibility in recognition of the severity of the condition and the importance of early-treatment.	
Wording	UCB Pharma	The remit defined by NICE reflects a population that is broader than the anticipated licence. In line with NICE processes the assessment population should align with the anticipated marketing authorisation [redacted]. It is not in NICE's remit to assess products outside their licence.	Thank you for your comment. The scope has not been updated. This is because the marketing authorisation wording is confidential and has not been confirmed, so may be subject to change. Considering this, the scope wording has been aligned with the population assessed in the clinical trial for doxecitine–doxribtimine. Doxecitine–doxribtimine will be evaluated within its marketing authorisation for TK2D.
	Salford Royal Hospital NCA	Yes	Thank you for your comment. No action required.
	The Lily Foundation and	The wording is reflective.	Thank you for your comment. No action required.

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	Metabolic Support UK		
	Genetic Alliance	The remit as drafted reflects the core questions of clinical and cost effectiveness. To ensure clarity, we suggest specifying that all patients must have a confirmed biallelic TK2 mutation and that the appraisal should cover people of any age and all recognised onset subtypes.	Thank you for your comment. No action required. This marketing authorisation wording is confidential and has not been confirmed so may be subject to change. Considering this, the scope wording has been aligned with the population assessed in the clinical trial for doxecitine–doxribtimine. Doxecitine–doxribtimine will be evaluated within its marketing authorisation for TK2D.

Comment 2: the draft scope

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Background information	UCB Pharma	TK2d is an ultra-rare disease in which there is a spectrum of phenotypes based on age of TK2d symptom onset, which to date is the best prognostic factor identified for rate of disease progression. The disease is characterised by premature death and involves progressive muscle weakness that manifests with variable rates of progression and functional impairment including respiratory difficulties, which can often result in mechanical ventilation. Additionally, feeding problems can occur with bulbar muscle weakness leading to dysphagia and a need for enteral feeding tubes in some patients.1–4 The description of the population subtypes as 'infantile', 'childhood' and 'late' onset are not defined consistently with the evolution of disease course understanding. While UCB recognises that the published literature uses a variety of age bands for clinical subtypes,3–5 based on the largest synthesis of disease course data, three age of onset subtypes should be defined: people with age of symptom onset ≤ 2 years, people with age of symptom onset > 2 and ≤ 12, and people with age of onset > 12.6–8 The Draft Scope states that "supportive care strategies aim to manage symptoms as they present, slow down disease progression and improve quality of life." It is more accurate to say that the current standard of care facilitates management of emerging symptoms but does not address the underlying disease.	Thank you for your comment. Comment noted. We have not updated the scope. This is consistent with published literature and other stakeholder consultation responses. The description of the subtypes remains broad in the scope. We have updated the scope to state that 'Supportive care strategies aim to manage symptoms as they present, but do not address the underlying cause of TK2D'.

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	Salford Royal Hospital NCA	Reduced phonation or complete loss of ability to speak to be added to the symptoms in childhood onset subgroup in the Background	Thank you for your comment. The scope background has been updated.
	The Lily Foundation and Metabolic Support UK	Accurate. We would also note that the literature shows that prevalence of TK2d is higher in younger ages and lower in higher ages, with one study showing a split of approximately 40/40/20 across the three recognised subgroups (Garone et al. 2018). We do however recognise that, as with many adult-onset mitochondrial diseases, these statistics may also be reflective of potential misdiagnoses and/or diagnostic delays amongst the older adult population whose symptoms may overlap with other muscle-related conditions. Garone et al. (2018). Retrospective natural history of thymidine kinase 2 deficiency. J Med Genet. Aug;55(8):515-521.	Thank you for your comment. Comment noted.
	Genetic Alliance	It may be helpful to note that eligibility requires genetic confirmation of a TK2 mutation and to clarify whether infants, children and adults with differing disease severities are all expected to receive the therapy.	Thank you for your comment. No action required. The marketing authorisation wording is confidential and has not been confirmed so may be subject to change. Considering this, the

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			scope wording has been aligned with the population assessed in the clinical trial for doxecitine–doxribtimine. Doxecitine–doxribtimine will be evaluated within its marketing authorisation for TK2D.
Population	UCB Pharma	No, the population is not defined appropriately. The [redacted]	Thank you for your comment. To align with the wording in the remit and to keep the anticipated license confidential, the population has not been changed. Doxecitine–doxribtimine will be appraised within its marketing authorisation for TK2D.
	Salford Royal Hospital NCA	Yes	Thank you for your comment. No action required.

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	The Lily Foundation and Metabolic Support UK	Yes	Thank you for your comment. No action required.
	Genetic Alliance	Yes. Defining the population as people of any age with TK2D is appropriate.	Thank you for your comment. No action required.
Subgroups	UCB Pharma	Age of symptom onset affects prognosis.[3–8] People with symptom onset [redacted] and people with symptom onset [redacted] have clinically distinct mortality and functional impairment profiles and will be presented as subgroups in the company submission.[3–8] [redacted]	Thank you for comment. To align with the wording in the remit and the population, the subgroups have not been changed. Doxecitine–doxribtimine will be appraised within its marketing authorisation for TK2D.
	Salford Royal Hospital NCA	The suggested subgroups are appropriate	Thank you for your comment. No action required.
	The Lily Foundation and Metabolic Support UK	We believe the subgroups suggested in the scope are appropriate and our experience aligns with that outlined; with the infantile onset being the most severe and devastating for patients and their families.	Thank you for your comment. No action required.

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		However, as a patient organisation that is dedicated to advocating for all mitochondrial disease patients, we do not feel qualified to comment on whether any subgroups should be considered separately.	
	Genetic Alliance	The three onset subtypes (infantile, childhood and late onset) are the key groups for separate analysis and reflect real-world experience. If data allow, it may also be informative to explore outcomes by baseline severity, for example whether patients are already receiving ventilatory support at treatment initiation. If any genotypic subgroups (e.g. specific mutations with known severity) are identifiable, those might be noted also.	Thank you for your comment. We have updated the scope to include the additional subgroups suggested.
Comparators	UCB Pharma	The comparator, best-supportive care, is appropriate.	Thank you for your comment. No action required.
	Salford Royal Hospital NCA	Established standard of care is supportive treatment and they are all included	Thank you for your comment. No action required.
	The Lily Foundation and Metabolic Support UK	Yes, all comparators have been included as standard clinical management and supportive care delivered by the multidisciplinary team is currently the only option for people affected by TK2d.	Thank you for your comment. No action required.
	Genetic Alliance	Yes, to our knowledge this section of the scope appears accurate, although we suggest that 'established clinical management without' could be defined explicitly as all supportive care measures routinely used in TK2D. For example, comparators may include respiratory support (e.g. ventilation, oxygen) when needed, nutritional support when swallowing fails (gastrostomy feeding tubes), and mobility aids/physiotherapy. This could also help clarify that while certain supplements, such as coenzyme Q10 and other vitamins/antioxidants ('mito cocktails'), are sometimes still	Thank you for your comment. The comparator section has not been updated to ensure that the scope is broad enough to capture all treatments and supportive

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		provided in practice for other mitochondrial diseases, there is no strong evidence for their benefit. https://journals.lww.com/co-pediatrics/abstract/2020/12000/mitochondrial_medicine_therapies__rationale,.2.aspx	measures that may be used by people with TK2D. However, we have updated the current treatment paragraph of the background section to more explicitly describe all the supportive care measures routinely used in TK2D.
Outcomes	UCB Pharma	The outcomes listed are appropriate.	Thank you for your comment. No action required.
	Salford Royal Hospital NCA	Appropriate	Thank you for your comment. No action required.
	The Lily Foundation and Metabolic Support UK	People living with TK2d and their carers often comment on the impact of (muscle) fatigue and loss of independence (as also evidenced during the 2022 FDA Listening Session on TK2d https://umdf.org/tk2d-patient-listening-session-january-2022/.) This may be included as part of some of the broader outcomes listed in the draft scope; however, ideally we would like to see (muscle) fatigue and loss of independence addressed as separate outcomes as these outcomes are what matter most to people living with TK2d.	Thank you for your comment. Loss of independence will likely be captured within outcome measures already listed in the scope. But we have updated the scope to

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		In addition, we would encourage the inclusion of neurological outcome measures, such as seizures, encephalopathy and cognitive impairment, as they have been reported in the published literature. Though these are much lower in prevalence when compared to muscle symptoms, they still result in significant impact on a person's quality of life (Berardo et al. 2022). Berardo et al. (2022). Advances in Thymidine Kinase 2 Deficiency: Clinical Aspects, Translational Progress, and Emerging Therapies. J Neuromuscul Dis. 2022 Mar 1;9(2):225–235. We would also like to see the inclusion of HRQoL measures that not only measure the impact on TK2d on the patient, but also in terms of the burden on the caregiver. The nature of TK2d means that most affected individuals completely lose their independence and are reliant on caregivers on a full-time basis. This has a serious impact on the caregiver, with results from our poster presented at the 2025 MDA conference showing that most caregivers (68.8%) spent ≥75 hours per week caregiving (Yeske et al. 2025). The negative impact of caring was reported across all domains, with the constant care burden affecting every aspect of caregivers' lives, from social and leisure activities, physical health, finances, mood and relationships. Parents and caregivers asked to describe the experience of caring for someone with TK2d used the word 'exhausting' most frequently, whilst expressing the persistent stress and emotional burnout that comes from caring with an individual with a severe, life-limiting illness. Yeske et al. (2025). Burden and impact of caring for those with thymidine kinase 2 deficiency (TK2d): results from the Assessment of TK2d Patient Perspectives (ATP) study. Retrieved via: https://www.mdaconference.org/abstract-library/burden-and-impact-of-caring-	include fatigue as an outcome. We have updated the scope to include neurological function as an outcome measure. We have updated the scope to specify the health-related quality of life outcome relates to both people with TK2D and their carers.

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		for-those-with-thymidine-kinase-2-deficiency-tk2d-results-from-the-assessment-of-tk2d-patient-perspectives-atp-study/	
	Genetic Alliance	The outcome measures listed cover the main clinical domains. We would welcome the addition of measures of functional milestones such as sitting and walking unaided, patient-reported fatigue or pain, and caregiver or family quality of life. Including these real-life measures will ensure that the evaluation captures what matters most to people affected by the condition. https://pmc.ncbi.nlm.nih.gov/articles/PMC6073909/	Thank you for your comment. Functional milestones such as sitting and walking are captured within the motor function outcome measure. We have updated the scope to specify the health-related quality of life outcome relates to both people with TK2D and their carers.
Equality	UCB Pharma	TK2d causes high levels of disability and profound quality of life and economic effects on the people with the disease, their carers and their families.9–12 Doxecitine and doxribtimine has the potential to substantially reduce support needs for people with TK2d and thus reduce inequality in England and Wales.6,13 In addition to reducing inequality because of disability, many children affected by TK2d have nursing mothers because the age of onset is frequently in the first two years of life. Doxecitine and doxribtimine has the potential to reduce inequality for nursing mothers, who are protected under equalities legislation.	Thank you for your comment. Comment noted. Where appropriate, the committee will consider the impact the recommendation may have for people with protected characteristics and on

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			the equality issues raised. The committee will also consider the impact of this condition on carers of young children and the associated carer burden during this appraisal.
	Salford Royal Hospital NCA	Draft covers all the patients affected with the condition	Thank you for your comment. No action required.
	The Lily Foundation and Metabolic Support UK	In terms of geographical inequality, we are aware that a new drug application for this product has been accepted by the FDA, and granted priority review. This means that a decision about potential approval could come as early as August 2025 (https://umdf.org/mar25-umdf-newsletter/). If approved, this would represent a geographical inequality in that people living with the same condition in the USA would gain access to a drug not available to patients in England. In addition, we would like to note that many people who live with TK2d are full-time ventilator dependant and so require access to a functioning electricity supply at all times. Families living in rural or remote areas of England, such as Devon and Cornwall, may therefore be more vulnerable to power outages, leaving them at greater risk of succumbing to this life-limiting disorder if	Thank you for your comment. Where appropriate, the committee will consider the impact the recommendation may have on the equality issues raised.

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		unable to access a functioning electricity supply, whilst also living with greater levels of anxiety and uncertainty related to this.	
	Genetic Alliance	The draft remit and scope do not exclude any protected groups by age, sex or disability. In practice, access to genetic testing and specialist centres may vary by region or socioeconomic status. Monitoring for any geographic or social inequalities in access to diagnosis and treatment would help to ensure that all eligible patients have fair and timely access to	Thank you for your comment. Where appropriate, the committee will consider the impact the recommendation may have on the equality issues raised.
Other considerations	Salford Royal Hospital NCA	None	Thank you for your comment. No action required.
	Genetic Alliance	No comments	Thank you for your comment. No action required.
Questions for consultation	UCB Pharma	**1. How many people have TK2D in England, and how many would be offered doxecitine–doxribtimine?** The estimated prevalence of TK2d is 1.64 per million population.[14] The population of England and Wales is estimated at 60.9 million people.[15] Therefore, the estimated number of people eligible for treatment with doxecitine and doxribtimine in the UK will be less than 100.[14,15] Given high rates of mortality, diagnostic delay and misdiagnoses, the number of people offered doxecitine and doxribtimine will be lower than the estimated prevalence.	Thank you for your comment. Comment noted.

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		2. What are the subtypes of TK2D? Are there any differences in the cause of TK2D between subtypes, for example, genetic mutations? What is the proportion (or the number) of people in England with each TK2D subtype? The subtypes are as described in the Draft Scope; however, these should be defined by age of symptom onset rather than descriptive terms as this avoids confusion caused by the various descriptive definitions that have been used in the literature. More than 50 *TK2* mutations have been linked to TK2d. In general, published data suggest a poor correlation between genotype and phenotype. In a cohort of 53 patients with TK2d in Spain, two genetic variants noted in patients with an age of TK2d symptom onset >12 years were reported at a higher prevalence than expected.[5,16–25] Ceballos et al. (2024) observed that these two genetic variants were up to 86 times more prevalent in populations of Spanish descent than in other populations.[5] These variants may not generalise to the patient population in the UK. Two reviews found that approximately 85% of people with TK2d had an age of onset at or before age 12.[3,4]	Thank you for your comment. Comment noted.
		3. What population would be expected to have doxecitine–doxribtimine? Would doxecitine–doxribtimine be suitable for all people with TK2D? Do you anticipate this treatment to be used in the whole population or for a particular subgroup, for example, by TK2D subtype? [redacted]	Thank you for your comment. Comment noted.

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		[redacted]	
		4. What is considered established clinical management for TK2D? Where do you consider doxecitine–doxribtimine will fit into the existing care pathway for TK2D? Doxecitine and doxribtimine will replace best supportive care within the licensed population. Best supportive care is inadequate and does not address the underlying disease.	Thank you for your comment. Comment noted.
		5. How is TK2D diagnosed? Are the genetic tests to establish the correct diagnosis of TK2D a standard practice in the NHS? If so, what are they? TK2d is diagnosed based on a detailed patient history, clinical examination, laboratory and genetic tests.[1] Clinical features suggestive of TK2d vary somewhat depending on the age of TK2d symptom onset. In patients with an onset before 1 to 2 years, the typical clinical picture is hypotonia, rapidly progressive muscle weakness, loss of previously acquired motor skills, respiratory impairment, intestinal dysmotility, failure to thrive; up to 30% of patients have neurological symptoms such as encephalopathy, seizures, cognitive impairment, hearing loss, and some patients exhibit cardiomyopathy.[1, 3, 26] In patients that have symptom onset after 1 to 2 years and before 12 years, the prominent clinical feature is progressive proximal muscle weakness which typically impacts gross motor function such as ambulation; dysphagia, facial muscle weakness including ptosis, restrictive lung disease; neurologic symptoms can be seen but are generally less common and other non-myopathic symptoms can include cardiac arrhythmias	Thank you for your comment. Comment noted.

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		and multiple bone fractures.[1, 3, 26] The gold standard for confirming TK2d is based on genetic testing which may reveal pathologic variants in the nuclear *TK2* gene.[27] Wang and colleagues note that regardless of age of TK2d symptom onset, the genetic basis for a diagnosis of TK2d is biallelic pathogenic variants or likely pathogenic variants in the *TK2* gene.[26] Genetic testing in the UK includes whole genome/exome sequencing and broad multi-gene panels. **6. Is a confirmed genetic mutation in the TK2 gene required before the use of doxecitine–doxribtimine?** [redacted] **7. Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope?** The outcomes listed are appropriate. **8. Are there any subgroups of people in whom doxecitine–doxribtimine is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Clinical and cost-effectiveness will be presented for the licensed population in total and by age of onset [redacted] subgroups. **9. Is there any data/evidence available on how long people live with TK2D/the impact of TK2D on quality of life? If so, is this data available by subtype of TK2D (infantile, childhood or late-onset)?**	Thank you for your comment. Comment noted. Thank you for your comment. No action required Thank you for your comment. Comment noted.

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		What are the differences in quality and length of life for those with different TK2D subtypes? Yes, there are many published papers that detail the effect of TK2d on length and quality of life.[1, 3, 9–12, 26]	Thank you for your comment. Comment noted.
		10. Please select from the following, will doxecitine–doxribtimine be: **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** D. It is the company's understanding that prescription initiation will be specifically within highly specialised mitochondrial services and that there is the potential for commissioning access and follow up via specialised neuromuscular centres.	Thank you for your comment. Comment noted.
		11. Would doxecitine–doxribtimine be a candidate for managed access? Given the ultra-rarity of TK2d, it is unlikely that UK-specific data collection through a managed access agreement would sufficiently resolve uncertainty in the company submission for doxecitine and doxribtimine. Low prevalence and incidence, combined with high mortality and substantial misdiagnosis and diagnostic delay mean that observed people receiving doxecitine and doxribtimine will be below estimated prevalence.	Thank you for your comment. Comment noted.

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		UCB will consider a managed access agreement and finalise plans before the company evidence submission. UCB anticipate that IMF interim funding is more likely to be appropriate for doxecitine and doxribtimine than IMF with managed access and evidence generation. **References** 1. Berardo A, Domínguez-González C, Engelstad K, *et al.* Advances in Thymidine Kinase 2 Deficiency: Clinical Aspects, Translational Progress, and Emerging Therapies. *J Neuromuscul Dis* 2022. 9: 225–235. 2. Domínguez-González C, Madruga-Garrido M, Mavillard F, *et al.* Deoxynucleoside Therapy for Thymidine Kinase 2–Deficient Myopathy. *Ann Neurol* 2019. 86: 293. 3. Garone C, Taylor RW, Nascimento A, *et al.* Retrospective natural history of thymidine kinase 2 deficiency. *J Med Genet* 2018. 55: 515–521. 4. Wang J, Kim E, Dai H, *et al.* Clinical and molecular spectrum of thymidine kinase 2-related mtDNA maintenance defect. *Mol Genet Metab* 2018. 124: 124–130. 5. Ceballos F, Serrano-Lorenzo P, Bermejo-Guerrero L, *et al.* Clinical and Genetic Analysis of Patients With TK2 Deficiency. *Neurol Genet* 2024. 10: e200138. 6. Garone C, Hirano M, Haas R, *et al.* Functional Outcomes in Patients with Thymidine Kinase 2 Deficiency Aged ≤12 Years at Symptom Onset Who Received Pyrimidine Nucleos(t)ide Therapy. *MDA Clinical & Scientific Conference 2025* 2025. at <https://www.mdaconference.org/abstract-library/functional-outcomes-in-patients-with-thymidine-kinase-2-deficiency-aged-≤12-years-at-symptom-onset-who-received-pyrimidine-nucleostide-therapy/>	

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		7. Scaglia F, Hirano M, Garone C, *et al.* Survival and Functional Outcomes in Patients with Thymidine Kinase 2 Deficiency Aged >12 Years at Symptom Onset Who Received Pyrimidine Nucleos(t)ides. *MDA Clinical & Scientific Conference 2025* 2025. at <https://www.mdaconference.org/abstract-library/survival-and-functional-outcomes-in-patients-with-thymidine-kinase-2-deficiency-aged-12-years-at-symptom-onset-who-received-pyrimidine-nucleostides/> 8. Domínguez-González C, Hirano M, Nascimento A, *et al.* The Disease Course of Untreated Patients with Thymidine Kinase 2 Deficiency (TK2d) Aged >12 Years at TK2d Symptom Onset: Findings from the Largest International TK2d Dataset. 2025. at <https://www.aan.com/msa/Public/Events/AbstractDetails/59735> 9. Amtmann D, Gammaitoni AR, Galer BS, *et al.* The impact of TK2 deficiency syndrome and its treatment by nucleoside therapy on quality of life. *Mitochondrion* 2023. 68: 1–9. 10. Balcells C, Waller K, Yeske PE, *et al.* Patient co-creation and collaboration in thymidine kinase 2 deficiency (TK2d): Incorporating a project steering committee into a qualitative observational study. 2023. 11. Balcells C, Karaa A, Waller K, *et al.* Patient experiences of thymidine kinase 2 deficiency (TK2d): preliminary results from an online survey conducted in partnership with the patient community. 2024. 12. United Mitochondrial Disease Foundation. TK2d Patient Listening Session – January 2022 | UMDF. 2022. at <https://umdf.org/tk2d-patient-listening-session-january-2022/> 13. Hirano M, Garone C, Haas R, *et al.* Survival Analyses in Patients with Thymidine Kinase 2 Deficiency Aged ≤12 Years at Symptom Onset Who Received Pyrimidine Nucleos(t)ide Therapy. *MDA Clinical & Scientific Conference 2025* 2025. at	

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	Salford Royal Hospital NCA	None	Thank you for your comment. No action required.
	The Lily Foundation and Metabolic Support UK	**1. How many people have TK2D in England, and how many would be offered doxecitine–doxribtimine?** TK2d is an ultra-rare condition. We understand that there are approximately 10-20 patients living with TK2d in England, of which approximately 2/3rds were symptomatic <12 years of age. Out of the families we do or have supported in the past, a number of these have sadly lost children in infancy due to the severe nature of this subgroup, further underlining the detrimental impacts of the condition.	Thank you for your comment. Comment noted. To be considered as part of the evaluation, the committee would welcome submissions from stakeholders that

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		2. What are the subtypes of TK2D? Are there any differences in the cause of TK2D between subtypes, for example, genetic mutations? What is the proportion (or the number) of people in England with each TK2D subtype? As a patient advocacy organisation we would leave these discussions to expert clinicians who would be most suited to answer this question. As previously noted, we are aware of previous publications suggesting a 40/40/20 split among the severity subtypes (Garone et al. 2018), but we also note that misdiagnosis is more common among individuals with late-onset, which may neutralise this split. **3. What population would be expected to have doxecitine–doxribtimine? Would doxecitine–doxribtimine be suitable for all people with TK2D? Do you anticipate this treatment to be used in the whole population or for a particular subgroup, for example, by TK2D subtype?** As previously noted, this is the first disease-modifying treatment for people with TK2d. As a patient organisation that believes 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. **4. What is considered established clinical management for TK2D? Where do you consider doxecitine–doxribtimine will fit into the existing care pathway for TK2D?**	outline the impact that TK2D has on patients and carers. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

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		We would defer to clinicians here; however, given that established clinical management consists of supportive care only, the approval of doxecitine-doxribtimine will complement the existing care pathway, offering for the first time an option to treat the condition rather than just managing the symptoms. **5. How is TK2D diagnosed? Are the genetic tests to establish the correct diagnosis of TK2D a standard practice in the NHS? If so, what are they?** Again, we would defer to clinicians for the details, although we can confirm that there is a standard testing pipeline established within the NHS to test for known genes responsible for causing mitochondrial diseases including TK2D. **6. Is a confirmed genetic mutation in the TK2 gene required before the use of doxecitine–doxribtimine?** As far as we are aware this is correct. **7. Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope?** We believe that the outcomes are appropriate and would draw particular importance to outcomes related to muscle function, given that TK2d is primarily a mitochondrial myopathy. During the FDA listening session in 2022, one hundred per cent of those surveyed chose muscle weakness as one of the symptoms that most impact daily quality of life. Of those, over 80% cited 'reduced muscle weakness' as a top priority for any intervention that aimed to reduce symptoms of the condition. https://umdf.org/tk2d-patient-listening-session-january-2022/	Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted. We have updated the scope to specify the health-related quality of life outcome relates to

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		As previously stated, we also strongly advocate for the inclusion of any outcomes that not only examine the quality of life of both individuals with a diagnosis of TK2d, but also of those with caregiving responsibilities. **8. Are there any subgroups of people in whom doxecitine–doxribtimine is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Please refer back to the previous answers given above. **9. Is there any data/evidence available on how long people live with TK2D/the impact of TK2D on quality of life? If so, is this data available by subtype of TK2D (infantile, childhood or late-onset)? What are the differences in quality and length of life for those with different TK2D subtypes?** The previously cited paper by Garone et al. (2018) details the 3 main subtypes of TK2d and identifies that each are associated with variable rates of survival, with the infant onset leading to early mortality within 1-2 years. The childhood onset subtype has been shown to be associated with moderate to severe progression and a survival rate of least 13 years following onset of symptoms. Finally, the late-onset subtype is associated with a slower progression and patients may be expected to live for around 23 years following symptom onset. 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. Our survey found that most patients (78.1%) needed home modifications and support to help with daily activities, whilst 12.5%	both people with TK2D and theirs carers. To be considered as part of the evaluation, the committee would welcome submissions from stakeholders that outline the impact that TK2D has on patients and carers. Thank you for your comment. Comment noted. Thank you for your comment. Comment noted.

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		required full time medical support. Moreover, the clinical manifestations of the disease led to debilitating physical impacts and severe psychological strain, with 25/32 respondents reporting that TK2d had either a 'somewhat negative' or 'extremely negative' impact on their mood (Yeske et al. 2025)	
		10. Please select from the following, will doxecitine–doxribtimine be: a) **Prescribed in primary care with routine follow-up in primary care** b) **Prescribed in secondary care with routine follow-up in primary care** c) **Prescribed in secondary care with routine follow-up in secondary care** d) **Other (please give details):** Please refer to clinicians	Thank you for your comment. Comment noted.
		11. Would doxecitine–doxribtimine be a candidate for managed access? We are not in a position to draw a conclusion on this but would provide full support to the community if this route was chosen.	Thank you for your comment. Comment noted.
		12. Do you consider that the use of doxecitine–doxribtimine can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? There is published evidence by Garone et al. (2018)	Thank you for your comment. Comment noted. To be considered as part of the evaluation,

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		showing that this treatment can offer meaningful improvements across all health domains. Not only did patients report improved physical health across domains including numbers of hospitalisations, mobility, fatigue, ability to swallow, and pain, they also reported improvements across psychosocial domains too. These included an improved ability to attend work or school, perform chores, and improvements in mood, social functioning and family relationships. The data also describes evidence that children who were previously unable to walk were now able to run and jump after 3 months of treatment. In this small study, over 50% of treated participants rated themselves as “Much improved” or “Very much improved” when compared to one year ago, compared to 0% in the untreated group. This type of evidence, though difficult to be included in a QALY calculation, is absolutely crucial to capture the real-life impact of treatment on patients and their families.	the committee would welcome submissions from stakeholders that outline the impact that TK2D has on patients and carers
		13. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. No comments	Thank you for your comment. No action required.
		14. 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:	Thank you for your comment. No action required.

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		• **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which doxecitine–doxribtimine 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.** No comments **15. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** No comments	Thank you for your comment. No action required.
	Genetic Alliance	**1. How many people have TK2D in England, and how many would be offered doxecitine–doxribtimine?** We estimate that fewer than 100 people in England are diagnosed with TK2D, reflecting the global prevalence of around 1.6 per million people (based on modelling data presented at ISPOR Europe in 2023 – link below). Actual numbers may be lower due to under-diagnosis, although it is hoped in coming years a national TK2D patient registry (possibly building on international registries like mitoSHARE) will help collect real-world data on survival, lung function and quality of life. The three recognised subtypes are infantile onset (symptoms before one year), childhood onset (one to 12 years) and late onset (after 12 years), with worldwide data suggesting an	Thank you for your comment. Comment noted.

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		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. www.ispor.org/docs/default-source/euro2023/tk2d-prevalenceispor-eu-poster24oct23128145-pdf.pdf?sfvrsn=6f123ff9_0 2. **Is a confirmed genetic mutation in the TK2 gene required before the use of doxecitine–doxribtimine?** Yes, as far as we are aware. Because TK2D is autosomal recessive, heterozygous carriers would not be included and eligibility will therefore require a genetically confirmed TK2 mutation, as per the trial, to avoid misdiagnosis and ensure correct targeting. We suggest that it may help to state whether all clinical severities and subtypes are expected to be treated under the license. If the evidence mainly comes from data from treatment of more severely affected infants and children, the scope could note whether mild/late-onset patients will also be offered therapy or if a restriction is anticipated. 3. **How is TK2D diagnosed? Are the genetic tests to establish the correct diagnosis of TK2D a standard practice in the NHS? If so, what are they?** We feel the wording is accurate but note it may also help to describe that TK2D is autosomal recessive and that genetic testing is needed for diagnosis. There are several routes to testing, including single gene, exome and biochemical testing routes, although we are not familiar enough with their routine use on the NHS to comment. Please see the below webpage that	Thank you for your comment. Comment noted. Doxecitine–doxribtimine will be evaluated within its marketing authorisation for TK2D. At the time of scoping, this has not been granted. Thank you for your comment. Comment noted. The scope has been updated to state that 'Thymidine kinase 2 deficiency (TK2D) is an autosomal recessive genetic disorder'. It has also been updated to

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		outlines the different types of test for TK2D. Muscle biopsy and certain imaging may also be used. https://www.rarediseaseadvisor.com/hcp-resource/thymidine-kinase-2-deficiency-testing 4. **Please select from the following, will doxecitine–doxribtimine be:** a) Prescribed in primary care with routine follow-up in primary care b) Prescribed in secondary care with routine follow-up in primary care c) Prescribed in secondary care with routine follow-up in secondary care d) Other (please give details**):** If approved, DoxTM would likely be started in a specialist centre (e.g. an NHS Highly Specialised Mitochondrial Service) with experience in mitochondrial myopathies as follow-up may involve local care (e.g. oxygen therapy clinics, dietetics) but with periodic review by specialists. For these reasons, while clinicians might be better positioned to comment, we feel that option (C) seems most realistic (it may begin as hospital-only due to the need for close monitoring then possibly shared with community teams).	note that 'Appropriate testing is needed to confirm a diagnosis of TK2D'. Thank you for your comment. Comment noted.

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

N/A