**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Hydromethylthionine mesylate for treating mild cognitive impairment or mild or moderate dementia caused by Alzheimer's disease [ID6343]

## Response to stakeholder organisation comments on the draft remit and draft scope

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

### Comment 1: the draft remit and proposed process

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| Appropriateness of an evaluation and proposed evaluation route | TauRx Therapeutics Management Ltd. | Single technology appraisal is the most appropriate evaluation method considering NICE will evaluate a single new technology.<br>There are currently no approved disease modifying therapies (DMTs) for early stages Alzheimer's disease, [redacted] A high unmet need currently exists for treatments able to modify disease progression safely and which can be delivered to patients within the framework of existing NHS care pathways for dementia, thereby maximising potential patient access to treatment. | Thank you for your comment. This topic will proceed as an STA. No change to the scope required. |
| | Association of British Neurologists | We are concerned about the quality of evidence underpinning this submission. After multiple negative trials for this compound, the submission appears to be based on a posthoc subgroup analysis of secondary outcomes (some of which were not prespecified) in an open label extension. Our view is | Thank you for your comments. The appraisal committee will consider the quality of |

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| | | that this technology is therefore not suitable for full evaluation through this route. | evidence in its deliberations. No change to the scope required. |
| | Alzheimer's Research UK | It is unclear when the full phase 3 data will be published and available for scrutiny. Until then, it's impossible to say for sure whether Hydromethylthionine mesylate (HMTM) is an effective drug for people with Alzheimer's disease and if this topic is appropriate for NICE evaluation. | Thank you for your comment. The appraisal committee will consider the quality of evidence in its deliberations. No change to the scope required. |
| | Alzheimer's Society | We believe an evaluation is appropriate and that Single Technology Appraisal is an appropriate evaluation route. | Thank you for your comment. This topic will proceed as an STA. No change to the scope required. |
| | Dementia UK | Dementia UK believes this evaluation, and the evaluation route, to be appropriate. | Thank you for your comment. This topic will proceed as an STA. No change to the scope required. |
| | NHS England | NHS England agree that the STA route is the most appropriate evaluate route for hydromethylthionine mesylate. | Thank you for your comment. This topic will proceed as an STA. No change to the scope required. |

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| Wording | TauRx Therapeutics Management Ltd. | No. The appraisal will focus on [redacted] | Thank you for your comment. The scope covers the likely marketing authorisation of the technology under evaluation. In its submission, the company may decide to submit in a narrower population. No change to the scope required. |
| | Alzheimer's Society | Yes. | Thank you for your comment. No change to the scope required. |
| | Dementia UK | Yes, the wording seems appropriate. | Thank you for your comment. No change to the scope required. |
| | NHS England | Yes | Thank you for your comment. No change to the scope required. |
| Timing issues | TauRx Therapeutics Management Ltd. | With no treatments currently available for early AD stages, especially MCI-AD, there exists a critical and unmet medical need. Data are available from the LUCIDITY trial to show that delay in making hydromethylthionine mesylate available to patients currently affected by MCI-AD leads to worse treatment outcomes even when an effective dose is administered after a 12-month delay. | Thank you for your comment. NICE aims, where possible, to provide timely guidance in line with marketing authorisation. This topic has been scheduled |

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| | | Patients already face significant delays in gaining access to existing treatment pathways. It is therefore important for NICE to assess the potential for hydromethylthionine mesylate to offer a treatment capable of delaying early disease progression as soon as possible. As an oral treatment, with a positive safety profile, hydromethylthionine mesylate will have a substantially reduced requirement for the frequent, costly and burdensome patient visits to specialised treatment clinics and additional safety monitoring requirements that are associated with intravenous alternatives currently under consideration. | into the work programme. No change to the scope required. |
| | Alzheimer's Research UK | Dementia has significant impact on wider society, with the estimated cost of dementia in the UK reaching £25 billion and Alzheimer's disease being a leading cause of death in England. Therefore, any technology which can slow or delay disease progression, confirmed by Phase 3 data, should be appraised by NICE as a matter of urgency. | Thank you for your comment. NICE aims, where possible, to provide timely guidance in line with marketing authorisation. This topic has been scheduled into the work programme. No change to the scope required. |
| | Alzheimer's Society | As set out in the background, there is no cure for Alzheimer's disease and there are currently no disease modifying treatments approved for use in the UK.<br><br>The scale of dementia and the cost of dementia help illustrate the urgency of a disease modifying treatment for Alzheimer's disease.<br><br>There are currently around one million people with dementia in the UK, set to rise to 1.4million by 2040. By severity, there are 488,000 people with mild dementia; 366,000 people with moderate dementia; and 128,000 people with | Thank you for your comment. NICE aims, where possible, to provide timely guidance in line with marketing authorisation. This topic has been scheduled into the work |

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| | | severe dementia. By 2040, the number of people with severe dementia will have increased by 42%. Estimates for the total population of people with mild cognitive impairment (MCI) and early Alzheimer's disease ranges from 200,000 to 1.6million.<br><br>The total cost of dementia in the UK is £42billion. The total costs are made up of costs of unpaid care (£21.1bn), social care costs (£17.2bn), and healthcare costs (£7.1bn) (as well as costs of quality of life and economic losses). By 2040, the total cost of dementia will have risen to £90bn. Social care costs will have reached £40.7bn – nearly the total cost of dementia today.<br><br>Alzheimer's disease impacts every area of people's lives, from ability to communicate and socialise to mobility and independence. For many it can cause anxiety and depression, and in the later stages of disease progression will lead to people struggling with tasks of daily living. Ultimately, dementia will mean a person is increasingly reliant on social care and is likely to require residential care. There is a lack of support for people living with Alzheimer's disease with many people struggling to access the support that they need to help them in their daily lives. Alzheimer's disease also has a huge impact on the health and wellbeing of unpaid carers, with many reaching breaking point due to their caring responsibilities and the lack of support available.<br>People living with Alzheimer's disease desperately want more support to help them live with the condition. They want to be able to slow the progression of symptoms to improve their quality of life, to have more time to live a 'normal' life, and to spend more time with loved ones.<br><br>Approval of a DMT for Alzheimer's disease also has the potential to be a catalyst for transforming diagnosis for dementia. This is all-important given that at present, more than a third of people in England don't have a diagnosis and thus access to the information and support it can bring. A DMT could | programme. No change to the scope required. |

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| | | lead to healthcare system leaders increasing diagnostic capacity and improving access to an early diagnosis and subtype diagnosis, benefitting people by enabling them access to treatment where eligible, and other forms of support otherwise. The prospect of a treatment that slows progression could also challenge the perception among some that nothing can be done to support a person with dementia. | |
| | Dementia UK | Dementia UK believes the evaluation to have a high level of urgency for the NHS. One million people are set to be living with dementia in the UK by 2025, rising to more than two million by 2051, and it is the leading cause of death in England in Wales.i There is currently no disease modifying treatment for Alzheimer's disease, the most common form of dementia, approved for use on the NHS.<br><br>Alzheimer's disease is a progressive and lifelimiting condition. For many, receiving a diagnosis of Alzheimer's disease can instil fear and confusion, impacting not only the individual with the diagnosis but also those involved in their care, as well as their broader family and friends. Individuals and their families may live with the condition for many years during which each and every day can throw up new and complex challenges as symptoms progress and individuals and their families try to navigate a complex and disjointed health and social care system.<br><br>As well as having a large impact on the quality of life for people with dementia, and those who support them, dementia is extremely costly. It is estimated that the cost of dementia care will be £90 billion in 2040.ii<br><br>Dementia UK has undertaken consultation with people with lived experience of dementia through our advisory panel on the impact of disease modifying drugs for Alzheimer's and found they have concurred that a disease modifying treatment would be of great urgency. However, they wished to stress that this is only if the treatment is effective, and benefits are not | Thank you for your comment. NICE aims, where possible, to provide timely guidance in line with marketing authorisation. This topic has been scheduled into the work programme. No change to the scope required. |

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| | | outweighed by negative side effects. They also emphasised that disease modifying treatments are only one element of the support urgently needed for people with dementia.<br><br>Likewise, Dementia UK urges that broader postdiagnostic support that includes ensuring people and their families have timely access to dementia specialist support and addressing systemic problems within health and social care, remain the priority. It is also key that post-diagnostic support remains consistent across the country. | |
| | NHS England | NHS England acknowledge that hydromethylthionine mesylate is one of a number of new products coming for the treatment of dementia. Hydromethylthionine mesylate is expected to have a broader licence than lecanemab and donanemab and therefore we consider it a priority topic in line with the national focus on dementia. | Thank you for your comment. NICE aims, where possible, to provide timely guidance in line with marketing authorisation. This topic has been scheduled into the work programme. No change to the scope required. |
| Additional comments on the draft remit | - | - | - |

**Comment 2: the draft scope**

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| Background information | TauRx Therapeutics Management Ltd. | Regarding epidemiology estimates: Please consider that NICE previously reported an estimate for patients with [redacted] | Thank you for your comment. As the company have mentioned in response to a later comment, amyloid positivity is not expected to be a condition of treatment with hydromethylthionine mesylate. No change to the scope required. |
| | Alzheimer's Society | The 'Background' states that '*Approximately 210,000 people in England have mild cognitive impairment, present to the healthcare system, and have clinical suspicion of Alzheimer's disease*'. A recent paper from NHS England cited estimates for the total population of people with mild cognitive impairment (MCI) and early Alzheimer's disease from 200,000 to 1.6million.<br><br>The 'Background' states that '*The number of people with dementia in England was estimated as 748,000 in 2019, with 107,100 cases of mild and 206,300 cases of moderate dementia*'.<br><br>New estimates commissioned by Alzheimer's Society, published in May 2024, estimate that there are currently around one million people with dementia in the UK, set to rise to 1.4million by 2040. By severity, there are 488,000 people with mild dementia; 366,000 people with moderate dementia; and 128,000 people with severe dementia. In England, there are currently 826,000 people with dementia, set to rise to 1,183,000 by 2040. | Thank you for your comment. Epidemiology estimates vary. The scope has been updated to highlight this. The estimate for the number of people with dementia has been updated.<br><br>Thank you for providing more information on the control arm of the trial. The scope has been updated. |

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| | | In the section, “The technology”, it states that “*It [HMTM] has been studied in clinical trials compared with placebo in people with mild cognitive impairment and mild to moderate dementia caused by Alzheimer's disease*”.<br><br>It may be useful to consider that the control arm of the trial received a low dose of a compound related to HMTM called MTC, aiming to maintain blinding, as HMTM colours the urine. The low dose was assumed to be clinically inactive but analysis suggested some pharmacological effect. Due to this, results were compared with placebos from other trials (including the Alzheimer’s disease Neuroimaging Initiative database and other trials not specified). The reliability and validity of this experimental approach should be considered. | |
| | Dementia UK | The background information seems accurate.<br><br>Dementia UK recommends that the importance of the support from unpaid carers is stressed. Management of dementia symptoms often relies upon input from unpaid carers. While carers support groups are mentioned as an intervention within the background information, the support from carers themselves should be recognised explicitly as well, as well as the need for family carers to access specialist support for their own wellbeing. | Thank you for your comment. The background is intended to be a brief overview of the condition and its treatment. The appraisal committee will consider the wider impact of Alzheimer’s disease on carers in its deliberations. No change to the scope required. |
| | NHS England | We acknowledge that the estimate for MCI population comes from the NICE DSU Report. We note that the epidemiological figures presented are consistent across the scoping documents for lecanemab and donanemab. | Thank you for your comment. The scope has been updated to |

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| | | We agree that these figures are highly uncertain and would recommend emphasising this in the scoping document.<br><br>We wondered if the scoping document should reference ongoing Technology Appraisals (e.g. lecanemab and donanemab) under pharmacological management (subject to NICE evaluation). | highlight the variance in epidemiological estimates and NICE's ongoing appraisals of lecanemab and donanemab. |
| Population | TauRx Therapeutics Management Ltd. | No. The application will [redacted] focus on people with [redacted]. | Thank you for your comment. The scope covers the likely marketing authorisation of the technology under evaluation. In its submission, the company may decide to submit in a narrower population. No change to the scope required. |
| | Alzheimer's Research UK | The population is defined appropriately however, given the variability in clinical definitions and uses of mild cognitive impairment (MCI), the wording could be clarified as follows:<br><br>People with mild cognitive impairment caused by Alzheimer's disease or mild or moderate dementia caused by Alzheimer's disease.<br><br>There is a clear need for guidelines on the investigation and follow up of mild cognitive impairment (MCI) which has not yet been addressed in the NICE dementia guideline (NG97). There is huge variation in how the term MCI is applied in clinical practice which results in uncertainty for patients in terms of their prognosis and inefficiency for assessment and diagnostic services. | Thank you for your comment. NICE tries to keep titles succinct and consistent with previous appraisals. The current title is consistent with the ongoing appraisals of lecanemab and donanemab. No change to the scope required. |

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| | Alzheimer's Society | Yes. | Thank you. No change to the scope required. |
| | Dementia UK | Yes | Thank you. No change to the scope required. |
| | NHS England | We agree that the proposed population is reflective of the current trials for hydromethylthionine mesylate. | Thank you. No change to the scope required. |
| Subgroups | TauRx Therapeutics Management Ltd. | No. The application will [redacted] focus on people with [redacted]. | Thank you for your comment. The scope covers the likely marketing authorisation of the technology under evaluation. In its submission, the company may decide to submit in a narrower population. No change to the scope required. |
| | Alzheimer's Research UK | Suggested subgroups are appropriate. | Thank you. No change to the scope required. |
| | Alzheimer's Society | People with Down's syndrome and Alzheimer's disease.<br><br>People with familial/early onset Alzheimer's disease | Thank you for your comment. The subgroups assessed will be based on the available evidence. No |

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| | | | change to the scope required. |
| | Dementia UK | Dementia UK urges that people with Young Onset Dementia are a sub-group that is considered separately. Younger Alzheimer's disease symptom onset is associated with accelerated disease progression and tau spreading.iii People with Young Onset dementia have a longer survival time after diagnosis than people with later onset dementia, meaning they are more likely to see longer term benefits of disease modifying treatments.iv People with lived experience of dementia have stressed that those with Young Onset Dementia may also benefit further from prolonged independence and time for future planning, relative to those who are diagnosed with dementia at a later age. Thus, additional or different benefits and side effects for people with Young Onset Dementia should be considered separately from those who are over the age of 65.<br><br>Dementia UK would also be interested to know whether hydromethylthionine mesylate will have trials for rarer forms of dementia, which are also linked to the build-up of tau. Frontotemporal Dementia, Corticobasal Degeneration and Progressive Supranuclear Palsy dementia are all linked to the build-up of tau, and hydromethylthionine mesylate has found to potentially have clinical benefits for frontotemporal dementia.v For clarity we therefore believe that this appraisal should explicitly address the applicability of this treatment for dementias beyond Alzheimer's disease. | Thank you for your comment. The subgroups assessed will be based on the available evidence.<br><br>Note that, in this appraisal, NICE cannot assess hydromethylthionine mesylate for types of dementia outside the remit of the scope. No change to the scope required. |
| | NHS England | We would stress that sub-group analysis in mild cognitive impairment or mild or moderate dementia caused by Alzheimer's disease is notoriously difficult. The clinical trials are unlikely to be powered to show statistical significance in subgroups – but we agree the committee should explore these as part of the process. | Thank you for your comment. The committee will consider the quality of evidence in their deliberations. |

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| | | | No change to the scope required. |
| Comparators | TauRx Therapeutics Management Ltd. | No. [redacted]. Despite widespread availability of standard oral symptomatic treatments for AD, they will not be compared with hydromethylthionine mesylate as there is no evidence of treatment benefit [redacted] and there is minimal evidence of beneficial impact on long term clinical outcomes [1]. Anti-amyloid monoclonal antibody treatments (donanemab and lecanemab) are still under evaluation and cannot be considered according to standard NICE methodology as they are not established in clinical practice in the NHS. However, additional points of consideration regarding these treatments will be provided despite non-availability in NHS clinical practice and absence of publicly available cost-utility information by the time of submission. | Thank you for your comment. The scope covers the likely marketing authorisation of the technology under evaluation. In its submission, the company may decide to submit in a narrower population with different comparators. No change to the scope required. |
| | Alzheimer's Research UK | All relevant comparators have been included.<br><br>The comparators listed (excluding those currently under NICE evaluation) are standard treatments currently used in the NHS. | Thank you for your comment. No change to the scope required. |
| | Alzheimer's Society | Yes | Thank you for your comment. No change to the scope required. |
| | Dementia UK | Dementia UK has no comments on the comparators. | Thank you for your comment. No change to the scope required. |

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| | NHS England | The comparators look correct to us – noting (as the draft scope does) that the appraisal of donanemab and lecanemab are ongoing. | Thank you for your comment. No change to the scope required. |
| Outcomes | TauRx Therapeutics Management Ltd. | No. Within the clinical trial outcome measures list that was supplied, those that need to be considered are:<br>• scales measuring cognitive and functional abilities<br>• loss of whole brain and hippocampal volume measured by MRI adverse effects of treatment | Thank you for your comment. The committee will consider which outcomes are most relevant. No change to the scope required. |
| | Alzheimer's Research UK | **Person-centred outcomes**<br>Alzheimer's Research UK commissioned research to understand the outcomes from new treatments that matter most to people. Among all demographics, family connections, driving, socialising, reading, and friendships rank as the highest priority outcomes for new treatments. These are not included in the Clinical Dementia Rating Scale (CDR) which clinicians and researchers employ to evaluate the severity of dementia. It is vitally important that HTA bodies and other stakeholders involved in the development and approval of new medicines consider the outcomes that matter to people with Alzheimer's disease when assessing new medicines.<br><br>**Health related carer quality of life**<br>• Given the disease profile, it is important NICE considers the effect of the treatment on health-related quality of life (QoL) of the carer.<br><br>• There are an estimated 700,000 informal carers caring for those living with dementia in the UK, and the annual economic cost of dementia to society due to informal care is £10.2 billion. Dementia effects carers | Thank you for your comment. All aspects of quality of life, including carer quality of life, will be considered in the evaluation if evidence allows. No change to the scope required. |

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| | | both mentally and physically. As well as having a major impact on daily living activities, we know informal carers are at a significant risk of depression and anxiety, leaving many socially isolated. Additionally, 48% of carers have a long-standing illness or disability.<br><br>• Given the impact that dementia has beyond the person with a disease such as Alzheimer's, and especially on carers, we believe carer health related quality of life (QoL) should be considered in a future appraisal to accurately assess the full value of a future treatment.<br><br>• NICE has previously taken into consideration carer health related QoL in their economic analysis for symptomatic treatment of Alzheimer's disease and should do so in this case. NICE should provide clear guidance on how Committees will consider caregivers' quality of life in the assessment process, including how to measure it.<br><br>• Benefits will potentially be shown in the long-term, particularly as greater care costs are associated with the later, moderate to severe stages of dementia, and will prove challenging to evaluate over the relative short-time period of the phase III clinical trials. Flexibility in cost-effectiveness assessment should be considered given the inherent nature of this data uncertainty.<br><br>**Over 60% of dementia carers are also women, presenting the case that a socially equitable consideration of quality of life must factor those of the carer.** | |

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| | Alzheimer's Society | It is also important for NICE to consider outcomes for unpaid carers, including outcomes relating to quality of life, health, and ability to work. | Thank you for your comment. All aspects of quality of life, including carer quality of life, will be considered in the evaluation if evidence allows. No change to the scope required. |
| | Dementia UK | It is important that outcomes are derived from the input of people with Alzheimer's disease and their carers. Alzheimer's disease is a highly complex, life-limiting disease with diverse impacts, frequent co-morbidities, and impacts beyond the person with Alzheimer's disease (i.e., on their family carers). People with lived experience of dementia have stressed that quality of life is extremely subjective, and often difficult to understand from an outside perspective. Due to this complexity, it is vital that there is input from people who are affected by the condition, as what is important to those with the condition may be different to what appears important to researchers.<br><br>For example, when we asked people with lived experience to review the suggested outcomes, they stressed that sensory issues should be given explicit mention, as this can have a very substantial impact on day-to-day life. For example, disruption of vision or hearing was reported to make various tasks required for independent living, such as reading, difficult.<br><br>Based on discussions we have had with people with lived experience, we would recommend that an indicator that captures the value of relationships is added; i.e, the extent to which relationships with family and friends are impacted by progression of Alzheimer's disease. | Thank you for your comment. All aspects of quality of life, including carer quality of life, will be considered in the evaluation if evidence allows. No change to the scope required. |

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| | | We also recommend that an indicator is added around family carers' quality of life, as this is often heavily impacted by the progression of Alzheimer's disease as well. Caring for someone with Alzheimer's disease can be immensely stressful, and have a physical and emotional toll upon the carer. Delayed progression may benefit carers through providing more time for planning (e.g getting legal and financial affairs in order), reduced emotional distress for the carer due to a slower progression of Alzheimer's disease, and reduced physical distress due to prolonged independence of the person with dementia. Dementia UK also urges that the financial cost of care is considered; e.g. carers being able to remain in employment for longer. | |
| | NHS England | The outcomes measured and the economic analysis approach outlined look appropriate | Thank you for your comment. No change to the scope required. |
| Equality | TauRx Therapeutics Management Ltd. | No equality issues are foreseen with the use of hydromethylthionine mesylate. This is because it can be administered within the current dementia care pathways in the NHS, which are based primarily on clinical diagnosis. There is no requirement for patient selection by amyloid-PET scan which would potentially create barriers to accessibility because of uneven availability across the NHS. As such, we do not envisage any inequalities arising from limitations in access to this technology.<br>There are no known diversity, equality or inclusion issues, including learning disabilities from data available. Ease of administration as an oral treatment minimises the chance of disadvantaged patient groups being excluded because of restriction of access to treatment or inability to tolerate repeated intravenous infusions. | Thank you for your comment. No change to the scope required. |
| | Alzheimer's Research UK | • Findings from Alzheimer's Research UK's Dementia Attitudes Monitor show that people from black, Asian and minority ethnic backgrounds are more likely to agree that 'dementia is an inevitable part of ageing'. | Thank you for your comment. The Equality Impact Assessment has been updated. |

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| | | Survey results also indicated that those from social grades DE (semi-skilled and unskilled manual workers, and those with no formal qualifications, state pensioners, casual and lowest grade workers, unemployed with state benefits only) were also more likely to agree with the statement. Less understanding and awareness of the diseases that cause dementia could result in people being less likely to come forward to seek diagnosis and treatment.<br>• In the UK, Black and South Asian people have an increased risk of dementia when compared to White people, while also having shorter survival post-diagnosis of AD**Error! Bookmark not defined.**. These d isparities are projected to become more pronounced, with a seven-fold increase in the prevalence of dementia in the UK expected among ethnic minorities, in comparison to a two-fold increase for the general population by 2050.<br>o Black and South Asian people are more likely to be diagnosed at a younger age and die earlier from dementia than White people (3 years earlier)**Error! Bookmark not defined.**.<br>• Discussion of equality issues relating to the target condition should include the consideration that there is higher prevalence of dementia in women, and over 60% of dementia carers are women.<br>• Other populations that are particularly impacted by dementia include individuals with Down's syndrome. The lifetime risk of Alzheimer's disease in people with Down's syndrome is more than 90% and is the leading cause of death in this population. | |
| | Alzheimer's Society | The differential effects of the drug on people based on their gender and ethnicity should be considered. | Thank you for your comment. The subgroups assessed will be based on the available evidence. No |

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| | | | change to the scope required. |
| | Dementia UK | Within the trials for hydromethylthionine mesylate, both people with dementia who live alone and people with dementia with certain comorbidities are excluded from being eligible to participate. While we appreciate the validity of the reasons behind this, a lack of understanding of how the drug may benefit people with dementia who live alone or have co-morbidities will likely generate unequal access to the technology in the event of approval. A significant number of people with dementia either live alone (estimated at 1 in 4) or have comorbidities (estimated at 9 out of 10).vi As such, these people being excluded from eligibility, or a lack of understanding of how the treatment may impact them differently, may result in significant disparities between people with Alzheimer's disease with and without additional disabilities and/or who have a partner or who live alone .<br><br>One of the consultation questions within the draft scope document is whether people with suspected mild cognitive impairment or mild or moderate dementia caused by Alzheimer's disease are routinely tested for amyloid pathology in the NHS. This is currently not the case, and the dependence upon pathology tests may well exacerbate inequalities when it comes to accessing treatment for Alzheimer's disease, as diagnosis rates are unequal across certain demographics.<br><br>In addition to marked regional differences in dementia diagnosis rates and system readiness to administer new treatments, there are underlying structural and cultural inequities in the recognition of symptoms and provision of care among diverse populations. This suggests that marginalised and underserved groups may be less likely to benefit. For instance, a 2018 study found that black people within the UK appear to be more at risk of dementia but less likely to receive a timely diagnosis. Additionally, research indicates | Thank you for your comment. The Equality Impact Assessment has been updated. |

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| | | that people of South Asian heritage within the UK are more likely to receive a dementia diagnosis at a later stage.<br><br>Similarly, those with Young Onset Dementia are statistically less likely to receive timely diagnosis than people with dementia over the age of 65: the average time to diagnose is 4.4 years in younger people compared to 2.2 years for people aged over 65.vii viii | |
| | NHS England | We do not think the draft scope needs changing in this regard. | Thank you for your comment. No change to the scope required. |
| Other considerations | TauRx Therapeutics Management Ltd. | Modelling from NHS/PSS perspective will not cover the broader societal value of hydromethylthionine mesylate, despite the considerable burden of AD on society and economy. | Thank you for your comment. The technology evaluation will consider all evidence on costs and benefits in the economic model. Costs outside of the NHS and Personal Social Services perspective fall outside of the reference case set out in NICE health technology evaluations: the manual. The manual notes that some technologies may have substantial benefits to other government |

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| | | | bodies. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website. No change to scope required. |

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| | Alzheimer's Research UK | **<u>Molecular biomarkers and diagnosis</u>**<br>• Receiving an accurate and early dementia diagnosis is important as it alleviates people's anxiety as they understand the problem and it allows them to plan and get the most from their lives. The current diagnostic pathway is resulting in patients either not receiving a disease-specific diagnosis or being diagnosed relatively late in disease progression.<br>• PET scans and CSF lumbar punctures are currently the clinically accepted 'gold standards' for diagnosing Alzheimer's disease, but although recommended in NICE guidelines in specific cases, these tests are currently offered to fewer than 2% of people in the UK seeking a dementia diagnosis.<br>• Alzheimer's Research UK would like this to be taken into account of economic modelling which suggest including the costs associated with diagnostic testing for amyloid in people with Alzheimer's disease who would not otherwise have been tested as part of STA.<br><br>***<u>Wider societal cost</u>***<br>• A true perspective of the full value of a treatment must also consider that dementia is different from many other disease areas in that costs are primarily picked up by individuals and families, not the state. This is driven by the relatively high prevalence of the disease and also the lack of treatment options. 1.1 billion hours are spent on unpaid informal care for dementia[12], and recent economic modelling suggests this equates to £10.2 billion[12]. In comparison, 342 million hours were spent on unpaid informal care for cancer, 618 million hours for coronary heart disease, and 450 million hours for stroke care.<br><br>• It could be many years before the full benefit of the technology for people living with dementia, their carers, and wider society are fully | Thank you for your comment. The technology evaluation will consider all evidence on costs and benefits in the economic model. Costs outside of the NHS and Personal Social Services perspective fall outside of the reference case set out in NICE health technology evaluations: the manual. The manual notes that some technologies may have substantial benefits to other government bodies. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit |

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| | | understood. Wider societal value will come in the form of keeping people out of supported care and in better health for many more years than is the present case.<br><br>• Approximately 55% of people living with dementia are in the mild stages, with 32% in the moderate stages and 12% in the severe stages. Slowing the progression of disease between the mild and severe stages of Alzheimer's would reduce the number of people requiring care who are living with Alzheimer's and present a cost benefit to the wider economy.<br><br>• Focusing narrowly on direct healthcare costs and benefits, with only limited consideration of social care and informal care costs, could result in an inaccurate assessment of the true value of the technology. Economic modelling with the London School of Economics showed that the full value of a disease modifying treatment for Alzheimer's disease is only demonstrated when a broader perspective of the savings across sectors, over time, is considered.<br><br>• More than a quarter of people with dementia are in care, and this has an annual cost to the economy of £10.8 billion. 60% of people receiving home-care services are living with dementia. In England and Wales, the number of people living with dementia who need palliative care will almost quadruple by 2040. | from the Department of Health and Social Care and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website. No change to scope required. |
| | Dementia UK | Dementia UK urges for there to be consideration of how eligibility for the drug would be determined, including how amyloid and tau pathology would be ascertained. Lumbar punctures and PET scans, the two methods for ascertaining cognitive impairment or dementia caused by Alzheimer's disease mentioned within the scoping document, are not part of routine clinical practice for diagnosing dementia. Furthermore, a positive PET scan for | Thank you for your comment. The committee will consider any equality issues related to access. The committee will also |

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| | | amyloid was one of the original criteria for participation in trials, and if this is required (i.e. lumbar punctures cannot be used as an alternative), that would even further limit screening routes.ix There is thus a critical question of whether sufficient infrastructure would be available to determine eligibility.<br><br>Availability, and training of, staff to carry out these tests is also a significant consideration. People with lived experience have informed us that lumbar punctures can be extremely uncomfortable, especially when performed by someone who is not skilled at performing them.<br><br>It is also worth considering the burden of administration of the treatment. People with lived experience indicated that the infusions required for Lecanemab and Donanemab would cause potential stress and burden, which the oral administration of Hydromethylthionine Mesylate would avoid. | consider whether there are any uncaptured benefits associated with hydromethylthionine mesylate. No change to the scope required. |
| Questions for consultation | TauRx Therapeutics Management Ltd. | *The eligibility criteria for the LUCIDITY trial of hydromethylthionine mesylate included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for hydromethylthionine mesylate in clinical practice?*<br><br>No. Because the primary target for treatment with hydromethylthionine mesylate is tau aggregation pathology, confirmation of presence of amyloid pathology is not a prerequisite for treatment.<br><br>In earlier trials in mild/moderate AD, there was no such requirement, and yet the treatment effects were comparable in subjects with therapeutic levels of drug exposure in the earlier trials. | Thank you for your comment. Comments noted. No change to the scope required. |

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| | | *Are people with suspected mild cognitive impairment or mild or moderate dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?*<br><br>No, amyloid confirmation is not routinely tested in current clinical practice and such tests are not commonly used. As less invasive diagnostic methods are developed, such as blood biomarkers, reliance on amyloid positivity by PET scan or lumbar punction to confirm diagnosis [redacted] is likely to decrease in the near term.<br><br>To be conservative from a cost-effectiveness perspective, however, costing for amyloid positivity confirmation will be included as a sensitivity analysis in both the cost-utility analysis and the budget impact model. | Thank you for your comment. Comments noted. No change to the scope required. |
| | | *Where do you consider hydromethylthionine mesylate will fit into the existing care pathway for Alzheimer's disease?*<br><br>At the early stages of dementia, i.e., potentially as treatment in patients clinically diagnosed [redacted].<br><br>The positive safety profile of hydromethylthionine mesylate ensures risk mitigation for patient usage in routine clinical practice, where full diagnostic testing may be unavailable, and is unnecessary for the mode of action of hydromethylthionine mesylate. | Thank you for your comment. Comments noted. No change to the scope required. |
| | | *Would hydromethylthionine mesylate be used as an add on treatment to established clinical management? Would hydromethylthionine mesylate be used in addition to AChE inhibitors, memantine, lecanemab or donanemab (subject to NICE's ongoing appraisals) or as an alternative?* | Thank you for your comment. Comments noted. No change to the scope required. |

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| | | No, it would not be used as an add-on.<br><br>*Please select from the following, would hydromethylthionine mesylate be:*<br>a. Prescribed in primary care with routine follow-up in primary care<br>b. Prescribed in secondary care with routine follow-up in primary care | |
| | | With hydromethylthionine mesylate's safety profile, ease of administration and lack of monitoring burden, treatment could be initiated either in primary and secondary care, with follow-up in primary care. If anti-amyloid monoclonal antibodies are approved for use in the NHS, this will generate considerable patient interest and likely add pressure to already long waiting times for access to secondary care assessment. An orally available alternative with minimal monitoring burden could present an attractive option. | Thank you for your comment. Comments noted. No change to the scope required. |
| | | Would hydromethylthionine mesylate be a candidate for managed access? | |
| | | [redacted]. | Thank you for your comment. Comments noted. No change to the scope required. |
| | | *Do you consider that the use of hydromethylthionine mesylate can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*<br><br>We recognise that the QoL estimates for both patients and caregivers capture the value of treatment for the purpose of traditional health-utility evaluation. | Thank you for your comment. Comments noted. No change to the scope required. |

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| | | This will therefore be provided. However, alleviation of the broad societal burden of dementia care is not fully captured by traditional methodology. | |
| | Alzheimer's Research UK | Until the full phase 3 data is published and available for scrutiny, Alzheimer's Research UK cannot appropriately comment on most of the scoping questions at this stage.<br><br>*The eligibility criteria for the LUCIDITY trial of hydromethylthionine mesylate included that people should have confirmed amyloid pathology. Is it expected that this will be a criterion for being eligible for hydromethylthionine mesylate in clinical practice? Are people with suspected mild cognitive impairment or mild or moderate dementia caused by Alzheimer's disease routinely tested for amyloid pathology in the NHS?*<br><br>To identify those people with MCI due to Alzheimer's disease or mild Alzheimer's disease the use of molecular biomarkers will be routinely required to determine amyloid positivity.<br>Diagnostic tests which are clinically validated are amyloid PET and CSF sample via lumbar puncture. They are recommended as a standard of care in NICE guidelines but are not currently commissioned as routine diagnostics across dementia services in England. In the 2021 Memory Assessment Services audit, only 2.2% of memory services had routine access to PET and CSF. In places where there is some access this is often via relationships with research institutions, often in neurology-led services. In 2021, psychiatrists reported that the main barriers they encountered to using diagnostic tests included limited infrastructure, lack of clinical expertise and a lack of commissioned services. | Thank you for your comment. Comments noted. No change to the scope required. |
| | Alzheimer's Society | People with suspected mild cognitive impairment or mild or moderate dementia caused by Alzheimer's disease are not currently routinely tested for amyloid pathology in the NHS. Currently only 2% of people diagnosed with | Thank you for your comment. Comments |

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| | | dementia receive a PET scan or CSF testing (and current PET scans don't test for amyloid) . | noted. No change to the scope required. |
| | Dementia UK | *Where do you consider hydromethylthionine mesylate will fit into the existing care pathway for Alzheimer's disease?*<br><br>Due to the fact that Alzheimer's disease is a progressive condition, but only those with mild to moderate cognitive impairment or dementia are eligible for Hydromethylthionine Mesylate, people should be offered this immediately following diagnosis (if it is approved). However, Dementia UK wishes to stress that there is no existing, standardised care pathway for dementia. Many of the core components of support which are meant to take place, such as primary care annual reviews, either do not take place or can be a mere tick-box exercise. This feeds into concerns about the infrastructure needed for the implementation of disease modifying treatments, as post-diagnostic support is currently often insufficient and fragmented, meaning access to drugs is unlikely to be timely and there may be insufficient monitoring or follow-up.<br><br>*Are there any subgroups of people in whom hydromethylthionine mesylate is expected to be more clinically effective and cost effective or other groups that should be examined separately?*<br><br>We would encourage the consideration of the cost effectiveness of Hydromethylthionine mesylate for people with Young Onset Dementia. People with Young Onset Dementia are less likely to die from other health conditions, and thus may experience benefits for longer. Furthermore, delayed or reduced progression of Alzheimer's Disease may have additional advantages for people with Young Onset Dementia, such as being able to stay in work for longer and more time for retirement planning. Conversely, negative side effects of treatment may be more impactful for those with Young Onset Dementia, for similar reasons (e.g. they are more likely to be in employment). As such, we urge that people with Young Onset Dementia are | Thank you for your comment. Comments noted. No change to the scope required.<br><br>Thank you for your comment. Comments noted. No change to the scope required. |

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| | | examined as a sub-group of people with mild or moderate cognitive impairment or dementia caused by Alzheimer's Disease.<br><br>*Would hydromethylthionine mesylate be a candidate for managed access?*<br><br>Dementia UK believes that managed access may be entirely appropriate for this drug. This is because of the benefits a diseasemodifying treatment may bring, but also the risks and uncertainties around this drug. For example, the LUCIDITY trial lasted for two years, and thus benefits and risks beyond this are unknown.x Furthermore, as noted above, it is currently unknown how this drug may benefit, or have risk for, people with dementia who have comorbidities – which constitutes the vast majority of people with dementia. Thus, Dementia UK thinks that hydromethylthionine mesylate would indeed be a candidate for ongoing evaluation from managed access. | Thank you for your comment. Comments noted. No change to the scope required. |
| | NHS England | Specialist Pharmacy Service horizon scanning has highlighted that the dementia pharmacological treatment pathway has the potential to be significantly reformed should the forthcoming pipeline of products in late-stage trials receive marketing authorisation(s) and subsequently be recommended as clinically and cost-effective by NICE. There are a number of key changes in service capacity and delivery, which would result from the availability of products such as donanemab and lecanemab, due to the requirements to identify, assess, test, deliver treatment and monitor patients. The administration and logistics of ensuring a seamless transition between these elements should also be considered carefully.<br><br>How hydromethylthionine mesylate will fit into this pathway needs to be considered under two scenarios (1) if donanemab and/or lecanemab are recommended by NICE and made available to the NHS and (2) if hydromethylthionine mesylate is compared to current standard of care if these treatments are not made available. | Thank you for your comment. Comments noted. No change to the scope required. |

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| Additional comments on the draft scope | TauRx Therapeutics Management Ltd. | Paragraph “The Technology” currently mentions hydromethylthionine mesylate (HMTM) has been studied in clinical trials compared with placebo. In order to keep blinding and avoid bias in the context of a randomized controlled trial, the actual comparator arm used in LUCIDITY trial is methylthioninium chloride (MTC), since HMTM and MTC both produce urinary colouration. | Thank you for providing more information on the control arm of the trial. The scope has been updated. |
| | Alzheimer’s Society | Any additional comments on the draft scope<br>Economic analysis<br>The scope states ‘*The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared’.* We would like to emphasise the importance of considering the impact over the long term.<br><br>The scope states ‘*The economic modelling should include the costs associated with diagnostic testing for amyloid in people with Alzheimer's disease who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.*’ The costs associated with testing for amyloid are very high, but it needs to be considered that this is due to a current baseline of very low levels of such testing. Increasing levels of testing will be needed not only for this drug if approved, but also for future drugs. There are 127 Alzheimer’s disease drugs in clinical trials, and more will be submitted for regulatory approval in the future. Diagnosis related costs should be considered in this context.<br><br>Expansion of diagnostic capacity is also needed, to help enable early diagnosis which would be required for access to a DMT, and this also has associated costs. Similarly, expansion of diagnostic capacity will also be | Thank you for your comment. Comments noted. No change to the scope required. |

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| | | needed for future DMTs, not just for this drug currently being considered, and will also benefit everyone with dementia, not only people who may be eligible for DMTs. An early diagnosis is important as it opens the door to information, care, support, and treatment, as well as planning for the future, and opportunities to participate in research. | |
| Comments on the stakeholder list | TauRx Therapeutics Management Ltd. | Additional Patient/ Carer Groups to include:<br>• Alzheimer's Disease International<br>• UK Alzheimer's Association<br>• Alzheimer Research UK<br>• Dementia UK<br>• Alzheimer Scotland<br>• Scottish Brain Sciences<br>• Alzheimer Europe<br>• Scottish Dementia Research Consortium<br>Patient/ Carer Groups to remove (since organization does not longer exist):<br>• Dementia Action Alliance<br>• National Neuroscience Advisory Group | Thank you for your comment. NICE's guidance applies to the NHS in England and Wales. As such, international patient organisations, or those from Scotland, are not usually included as stakeholders. Alzheimer's Association is an American organisation. Alzheimer's research UK and Dementia UK are both already included in the stakeholder list.<br>Both Dementia Action Alliance and National Neuroscience Advisory Group have been removed from the stakeholder list. |