Health Technology Briefing
May 2023

Hydromethylthionine mesylate for Alzheimer's disease

Company/Developer	TauRx Therapeutics Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 8208	NICE TSID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Hydromethylthionine mesylate is currently in clinical development for the treatment of Alzheimer's disease (AD). AD is a progressive neurological disease which is caused by loss of function and death of nerve cells in the brain. It is the most common type of dementia. One of the early symptoms of AD is mild cognitive impairment where a person may have difficulty with memory, reasoning, and attention. In the early stages the difficulties are significant enough to be noticed by the patient and their family or friends but not so severe as to affect their ability to carry out some everyday activities. There is currently no cure for AD and current treatment options aim to relieve the symptoms (including cognitive impairment) rather than stop progression of the disease.

Hydromethylthionine mesylate is a potent inhibitor of tau aggregation. Tau is a critical protein required for the normal function of brain cells. It has a very important role in stabilising the structure of the brain cell, and it also plays a role in energy, transport, and cell communication in the brain. Tau has a central role in Alzheimer's disease pathology. Ageing brain cells often have a reduced ability to clear cell waste, causing tau proteins to misfold and bind to the waste products. Tangles are formed when aggregated and misfolded tau stacks clump together. A build-up of tangles causes the cell to swell and burst. Once the brain cell is gone, there is no repairing or regaining it. They ultimately cause the irreversible cell damage in the brain associated with clinical dementia. Hydromethylthionine mesylate is administered as an oral tablet and if licensed, it would offer a treatment option targeting disease progression, rather than just easing the symptoms of the disease.

Proposed Indication

For the treatment of Alzheimer's disease (AD) in patients up to 90 years old.[1]

Technology

Description

Hydromethylthionine mesylate (TRx0237) is a potent inhibitor of tau aggregation in vitro and in vivo.[1,2] It is a stable crystalline form of hydromethylthionine, the reduced form of methylthionine.[3] Hydromethylthionine has been shown to reduce the tau pathology and behavioural impairments in tau transgenic mouse models.[4] It acts both by inhibiting tau aggregation and by disaggregating pathological tau oligomers and filaments.[3] Tau protein is a critical protein for the normal function of brain cells. It has a very important role in stabilising the structure of the brain cell, and it also plays a role in energy, transport, and cell communication in the brain. Ageing brain cells often have a reduced ability to clear cell waste, causing tau proteins to misfold and bind to the waste products. This misfolding and change in their shape initiates an autocatalytic or cascade response, where more free tau proteins are attracted to them in the same misfolded structure. The misfolded tau aggregates and forms paired helical filaments which are insoluble stacks which can no longer be cleared by the cell. This process rapidly accelerates, and fragments of these insoluble tau stacks (oligomers) can spread from neuron to neuron, before initiating process of tau aggregation in previously healthy neurons. The oligomers are toxic to synapses and correlate with dementia.[5,6] A build-up of tangles causes the cell to swell and burst. Once the brain cell has gone, there is no repairing or reforming it. This pathological process ultimately contributes to the irreversible cell damage in the brain associated with clinical dementia.[6]

Hydromethylthionine mesylate is in clinical development for the treatment of AD. The phase III clinical trial (NCT03446001; LUCIDITY) is designed to assess safety and efficacy of hydromethylthionine mesylate in patients with mild cognitive impairment due to AD and mild to moderate AD dementia. In this clinical trial, hydromethylthionine mesylate is administered twice daily as 4mg oral tablets for either 8mg/day or 16mg/day dose.[1,7]

Key Innovation

There is currently no cure for AD. Available medication temporarily eases symptoms of AD or slows down its progression in some people, but these drugs do not slow down or stop the progression of the underlying disease in the brain.[8] Tau aggregation is a promising target for disease-modifying AD therapy as it is a hallmark pathology of AD that correlates with AD clinical severity and progression.[3] Hydromethylthionine mesylate is a tau aggregation inhibitor shown to have exposure-dependent pharmacological activity on cognitive decline and brain atrophy in two completed phase III trials in mild/moderate AD.[9]

If licensed, hydromethylthionine mesylate would offer a treatment option targeting Alzheimer's disease progression, rather than just easing the symptoms of the disease.

Regulatory & Development Status

Hydromethylthionine mesylate does not currently have Marketing Authorisation in the EU/UK for any indication.

Hydromethylthionine mesylate has the following regulatory designations/awards:[10,11]

- An FDA Orphan drug designation in the USA in 2018 for the treatment of frontotemporal dementia
- An EMA Orphan designation in 2010 for treatment of behavioural variant frontotemporal dementia

Patient Group

Disease Area and Clinical Need

Dementia is the name for a set of symptoms associated with an ongoing decline of brain functioning. It can affect memory, thinking skills and other mental abilities. Dementia develops when the brain is damaged by diseases, including AD.[12] AD is a physical disease that affects the brain.[13] The exact cause of AD is not yet fully understood, however there are a number of factors which are thought to increase the risk of developing the condition. These include increasing age, a family history of the condition, lifestyle factors and conditions associated with cardiovascular disease. AD is a progressive condition, which means the symptoms develop gradually over many years and eventually become more severe. The first sign of AD is usually minor memory problems. As the condition develops, memory problems become more severe and further symptoms can develop such as confusion, disorientation, getting lost in familiar places, difficulty planning or making decisions and problems with speech and language.[12]

AD is the most common cause of dementia in the UK. It occurs most commonly among people over the age of 65. The risk of AD and other types of dementia increases with age, affecting an estimated 1 in 14 people over the age of 65 and 1 in every 6 people over the age of 80.[12] 944,000 patients are estimated to be living with dementia in the UK; this number is expected to grow rapidly over the next several decades.[14] In England (2021-22), there were 2,354 finished consultant episodes (FCE) and 1,180 admissions for dementia in AD (ICD-10 code F00). This resulted in 59,395 FCE bed days and 7 day cases.[15] Of all deaths registered in 2022 in England and Wales, 65,967 (11.4%) were due to dementia and AD.[16] The age-standardised mortality rate due to dementia and AD was significantly lower in males compared with females.[17]

Recommended Treatment Options

There is currently no cure for AD, but there are medicinal products available that can temporarily reduce the symptoms in patients with mild to moderate AD. The National Institute for Health and Care Excellence (NICE) recommends:[12,18]

- Acetylcholinesterase (AChE) inhibitors (donepezil, galantamine and rivastigmine) as monotherapies for managing mild to moderate AD
- Memantine is recommended for people with moderate AD who are intolerant of or have a contraindication to AChE inhibitors, or severe AD

Medicinal products for AD symptoms are only one part of the care package for people with dementia. Other treatments such as activities and support are important in helping people live well with dementia. Some of the activities include cognitive stimulation therapy, cognitive rehabilitation, reminiscence, and life story work.[19]

Clinical Trial Information

Trial	**LUCIDITY;** NCT03446001, EudraCT2017-003558-17; Randomized, Double-Blind, Placebo-Controlled, Three-Arm, 12-Month, Safety and Efficacy Study of TRx0237 Monotherapy in Subjects With Alzheimer's Disease Followed by a 12-Month Open-Label Treatment **Phase III** – active, not recruiting **Location(s):** 5 EU countries, UK, USA, and Canada **Primary completion date:** March 2022

Trial Design	Randomised, quadruple-masked, double-blind, placebo-controlled, parallel assignment
Population	N=598 (actual); patients aged up to 90 years with a diagnosis of Alzheimer's disease, encompassing probable Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease, and have had a documented PET scan that is positive for amyloid.
Intervention(s)	Oral hydromethylthionine mesylate 4mg tablets administered twice daily (for either 8mg/day or 16mg/day dose)
Comparator(s)	Placebo
Outcome(s)	**Primary outcome measures:** • Change from baseline on Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog_{11}) [time frame: baseline and 52 weeks]. • Change from baseline on Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL_{23}) [time frame: baseline and 52 weeks]. • Number of study participants with serious and non-serious adverse events [time frame: up to 52 weeks]. See trial record for full list of other outcomes.
Results (efficacy)	The mild cognitive impairment (MCI) group, which had baseline Mini Mental State Examination (MMSE) scores of 23, showed statistically significant improvements of 2 units over the pre-treatment baseline at 6 months (P=.0002), 12 months (P=.0391), and 18 months (P=.0473) on ADAS-Cog_{13} scale after treatment with 16-mg/day dose (n=105). Similarly, those with mild to moderate AD (n=147) demonstrated a 2.5-unit cognitive decline on ADAS-Cog_{13} in the first 9 months and no further decline over the following 9 months.[20] Additional findings showed statistically significant reductions in disease progression as measured by change in cognitive function (P=.0008) and brain atrophy (P<.0001) that were confirmed by comparisons of participants receiving the 16-mg/day dose against participants from the Alzheimer's Neuroimaging Initiative (ADNI) who were closest to the study population by age and clinical severity. These findings were consistent regardless of whether patients had MCI-AD or mild to moderate AD. Those treated with hydromethylthionine mesylate 16mg/day had a rate of progression of brain atrophy that was significantly less than in matched ADNI patients (P <.0001) and comparable to that seen in ADNI healthy aging subjects.[20]
Results (safety)	The therapy showed a safety profile that was consistent with previous trials, with no evidence of serious treatment-emergent adverse events or amyloid-related imaging abnormalities, known commonly as ARIA.[20]

Estimated Cost

The cost of hydromethylthionine mesylate is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Gantenerumab for treating early Alzheimer's disease (TA11072). Expected publication date to be confirmed.
- NICE technology appraisal awaiting development. Donanemab for treating symptomatic early Alzheimer's disease (TA11221). Expected publication date to be confirmed.
- NICE quality standard. Dementia (QS184). June 2019.
- NICE technology appraisal. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (TA217). March 2011. Updated June 2018.
- NICE guideline. Dementia: assessment, management and support for people living with dementia and their carers (NG97). June 2018.
- NICE guideline. Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset (NG16). October 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.

Other Guidance

- American Academy of Neurology. Practical guideline update: Mild cognitive impairment. 2017.[21]
- British Columbia Medical Journal. Cognitive Impairment Guideline. 2015.21.[22]
- National Institute on Aging. Alzheimer's Disease Diagnostic Guidelines. 2011.[23]
- European Journal of Neurology. EFNS guidelines for the diagnosis and management of Alzheimer's disease. 2010.[24]

Additional Information

TauRx Therapeutics Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

The company terminated clinical trial (NCT01626391) which was evaluating the safety of TRx0237 in patients already taking medications for mild and moderate Alzheimer's disease. This study has been terminated for administrative reasons only.

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