Health Technology Briefing
November 2022

Donanemab for treating early symptomatic Alzheimer's disease

Company/Developer	Eli Lilly and Company Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23843	NICE TSID: 10635	UKPS ID: 664738

Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

Summary

Donanemab is currently in clinical development for the treatment of early Alzheimer's disease (AD). AD is a progressive neurological disease which is caused by loss of function and death of neurones 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, attention. The difficulties are significant enough to be noticed by the patient and their family or friends but not enough to affect their ability to carry out some everyday activities. Current treatment options for AD aim to relieve the symptoms (including cognitive impairment) rather than stop progression of the disease.

Donanemab is a monoclonal antibody (a type of protein) that binds to deposited aggregates of beta-amyloid (Aβ) that have been implicated in the development of AD. This helps clear the existing amyloid deposits in the brain. Donanemab is administered intravenously and if licensed, would offer an additional treatment option for early AD that would potentially modify the underlying disease process rather than treating only the symptoms of the disease.

Proposed Indication

For the treatment of patients with early symptomatic Alzheimer's disease (AD).[1-5]

Technology

Description

Donanemab is a humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a. This biologic drug recognizes Aβ (p3-42), a pyroglutamate form of Aβ that is aggregated in amyloid plaques. Most Aβ antibodies in therapeutic development bind various soluble or insoluble species but have low affinity to deposited amyloid plaques. The rationale behind donanemab is that targeting deposited plaque itself is necessary to clear existing amyloid burden from the brain, rather than merely prevent deposition of new plaques or growth of existing plaques.[6,7]

In the phase II (NCT03367403) clinical trial, 700 milligram (mg) donanemab was administered intravenously (IV) every 4 weeks (Q4W) x 3 doses, then 1400 mg donanemab IV Q4W for up to 72 weeks.[1]

Key Innovation

There is currently no cure for AD. Available medication temporarily eases symptoms of AD in some people.[8] These drugs however do not slow down or stop the progression of the underlying disease in the brain.[9] Some previous plaque-binding antibodies have been abandoned because they caused microhaemorrhages in the brain. The Aβ specific IgG2a antibody (mE8) was reported to clear plaques in mice without causing microhaemorrhage.[6,7]

In the phase II trial, NCT03367403, donanemab showed significant slowing of decline in a composite measure of cognition and daily function in patients with early symptomatic AD compared to placebo. Donanemab also slowed the clinical progression of the disease, suggesting that this could potentially be a disease-modifying therapy.[10,11]

Regulatory & Development Status

Donanemab does not currently have marketing authorization in the EU/UK for any indication.

In June 2021, Food and Drug Administration (FDA) granted breakthrough therapy status of donanemab for AD.[12]

Patient Group

Disease Area and Clinical Need

Dementia is the name for a set of symptoms that includes memory loss and difficulties with thinking, problem-solving or language. Dementia develops when the brain is damaged by diseases, including AD. AD is a physical disease that affects the brain.[13] The exact cause of AD is not yet fully understood, however risk factors include: increasing age, a family history of the condition, untreated depression, 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.[14]

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.[14] 944,000 patients are estimated to be living with dementia in the UK, although only 517,412 are thought to have a confirmed diagnosis. There has been a 56% rise in the number of people diagnosed with dementia from 2010/11 to 2015/16.[15] The estimated cases of dementia overestimate the number of eligible patients for donanemab, which is indicated for early symptomatic AD.[a] The 2021-2022 Hospital Episode Statistics (HES) for England recorded a total of 2,354 finished consultant episodes (FCE) for dementia in AD (ICD-10 code: F00), resulting in 1,180 hospital admissions, 59,395 FCE bed days and 7 day cases.[16] Of all deaths registered in 2019 in England and Wales, 66,424 (12.5%) were due to dementia and AD. 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. National Institute for Health and Care Excellence (NICE) recommends:[14,18]

- Acetylcholinesterase (AChE) inhibitors (donepezil, galantamine and rivastigmine) as monotherapies for managing mild to moderate AD
- Memantine is recommended for people with moderate AD who cannot take or are unable to tolerate 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 – for the carer too, – are just as important in helping people live well with dementia. Some of the activities include: cognitive stimulation therapy, cognitive rehabilitation, reminiscence and life story work.[14]

Clinical Trial Information

Trial	NCT03367403; **TRAILBLAZER-ALZ;** Assessment of Safety, Tolerability and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease **Phase II –** Completed **Location(s):** US and Canada **Study Completion date:** September 2021
Trial Design	Randomised, double blind, parallel assignment
Population	N= 272 (actual); Subjects aged 60 to 85 years with gradual and progressive change in memory function reported by participants or informants for ≥ 6 months; A Mini Mental State Examination (MMSE) score of 20 to 28 (inclusive) at baseline or an acceptable historical flortaucipir Positron Emission Tomography (PET) scan within 6 months prior to baseline that meets the central read criteria.
Intervention(s)	Participants received 700mg donanemab intravenously Q4W x 3 doses, then 1400mg donanemab IV Q4W for up to 72 weeks.
Comparator(s)	Matched placebo IV Q4W for up to 72 weeks.
Outcome(s)	Change from baseline in the integrated Alzheimer's disease rating scale (iADRS) score [Time frame: baseline, 76 weeks]

[a] Information provided by Eli Lilly and Company Ltd

	See trial records for full list of other outcomes
Results (efficacy)	In patients with early Alzheimer's disease, donanemab resulted in a better composite score for cognition and for the ability to perform activities of daily living than placebo at 76 weeks, although results for secondary outcomes were mixed.[19]
Results (safety)	There was no significant difference between the donanemab group and the placebo group in the incidence of death or serious adverse events.[19]

Trial	NCT04437511; Eudra CT 2020-000077-25; **TRAILBLAZER-ALZ 2;** Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease **Phase III –** Active, not recruiting **Location(s):** 3 EU, UK, US, Canada, and other countries **Primary completion date:** April 2023
Trial Design	Randomised, double blind, parallel assignment
Population	N=1800 (estimated); Subjects aged 60 to 85 years with gradual and progressive change in memory function reported by participants or informants for ≥ 6 months; MMSE score of 20 to 28 (inclusive) at baseline
Intervention(s)	Donanemab given intravenously
Comparator(s)	Matched placebo
Outcome(s)	Change from baseline on the iADRS [Time frame: baseline, up to week 76] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT04640077; **TRAILBLAZER-EXT;** Donanemab Follow-On Study: Safety, Tolerability, And Efficacy in Symptomatic Alzheimer's Disease With Validation of Remote Neuropsychological Assessments **Phase II –** Active, not recruiting **Location(s):** US and Canada **Primary completion date:** September 2023
Trial Design	Non-randomised, open-label, sequential assignment
Population	N= 90 (actual); Subjects aged 60 to 90 years who participated in a double-blind treatment period of a sponsor-approved originating donanemab trial, for example the TRAILBLAZER-ALZ study.
Intervention(s)	Donanemab administered intravenously

Comparator(s)	-
Outcome(s)	Percentage of participants with one or more adverse events (AEs) or serious AEs [Time frame: up to 72 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT05108922; **TRAILBLAZER-ALZ 4;** A Phase 3, Open-Label, Parallel-Group, 2-Arm Study to Investigate Amyloid Plaque Clearance With Donanemab Compared With Aducanumab-avwa in Participants With Early Symptomatic Alzheimer's Disease **Phase III –** Active, not recruiting **Location(s):** US **Study Completion date:** July 2024
Trial Design	Randomised, open-label, parallel assignment
Population	N= 200 (estimated); Subjects aged 50 to 85 years with gradual and progressive change in memory function reported by the participant or informant for ≥6 months
Intervention(s)	Donanemab is administered IV Q4W
Comparator(s)	Aducanumab administered IV per label
Outcome(s)	Percentage of participants who reach complete amyloid plaque clearance on florbetapir F18 PET Scan (superiority) on donanemab versus aducanumab [Time frame: 6 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT05508789; **EudraCT 2021-006395-17; TRAILBLAZER-ALZ 5;** Global Study to Investigate Safety and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease **Phase III** – Recruiting **Location(s):** 7 EU countries and Asia **Primary completion date:** April 2027
Trial Design	Randomised, double blind, parallel assignment
Population	N= 1500 (estimated); Subjects aged 60 to 85 years with gradual and progressive change in memory function reported by the participant or informant for ≥6 months; A MMSE score of 20 to 28 (inclusive) at Day 601 or 1

Intervention(s)	Donanemab IV
Comparator(s)	Matched placebo
Outcome(s)	Change from baseline on the iADRS [Time frame: baseline, week 76] See trial record for full list other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of donanemab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Aducanumab for treating mild cognitive impairment and mild dementia caused by Alzheimer's disease (GID-TA10739). Expected publication date TBC.
- NICE technology appraisal awaiting development. Gantenerumab for treating early Alzheimer's disease (GID-TA11072). Expected publication date to be confirmed.
- NICE technology appraisal. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (TA217). 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.
- NICE quality standard. Dementia (QS184). June 2019

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.[20]
- British Columbia Medical Journal. Cognitive Impairment Guideline. 2015.[21]
- European Journal of Neurology. EFNS guidelines for the diagnosis and management of Alzheimer's disease. 2010.[22]

Additional Information

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