Health Technology Briefing
November 2021

Lecanemab for treating early Alzheimer's disease

Company/Developer	Eisai Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 8596	NICE ID: 10180	UKPS ID: 649953

Licensing and Market Availability Plans

Currently in Phase II/III trials.

Summary

Lecanemab 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, or visual depth perception. 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 everyday activities. Current treatment options for AD aim to relieve the symptoms (including cognitive impairment) rather than stop progression of the disease.

Lecanemab is a monoclonal antibody (a type of protein) that selectively binds and clears protofibrils, large highly-toxic soluble aggregates of beta-amyloid (Aβ) that have been implicated in the development of AD. Lecanemab is given through intravenous (IV) infusion and if licensed, would offer an additional treatment option for AD that would modify the underlying disease process rather than treating the symptoms of the disease.

Proposed Indication

Early Alzheimer's disease (AD).[1]

Technology

Description

Lecanemab (BAN2401) is the humanized IgG1 version of the mouse monoclonal antibody mAb158, which selectively binds to large, soluble Aβ protofibrils. mAb158 was found to reduce Aβ protofibrils in brain and cerebrospinal fluid (CSF) of Tg-ArcSwe mice. Subsequent studies in mouse neuron-glial co-cultures showed that mAb158 may protect neurons, i.e., reduce Aβ protofibril toxicity, by counteracting the pathological accumulation of these protofibrils in astrocytes.[2]

In the phase III trial (NCT03887455), lecanemab was administered as a IV infusion once every two weeks at a dose of 10mg/kg.[3]

Key Innovation

Reduction of Aβ protofibrils and Aβ plaque, as well as prevention of Aβ deposition before plaques develop, has been demonstrated using the murine version of lecanemab in animal models.[4]

The phase IIb clinical trial (NCT01767311) found that lecanemab treatment resulted in a dose-dependent and consistent reduction in clinical decline relative to placebo across a number of clinical endpoints according to Bayesian and frequentist approaches. These effects were accompanied by a dose-dependent reduction in brain amyloid PET over 18 months of treatment and were reinforced by additional cerebrospinal fluid (CSF) biomarker results. Taken together, the findings in this double-blind trial on multiple cognitive endpoints and biomarkers are supportive of the therapeutic concept for the targeting specific oligomeric species (protofibrils) in the process of pathophysiological amyloid accumulation in AD.[4]

Regulatory & Development Status

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

Lecanemab is also in clinical development for pre-clinical AD.[a]

In June 2021, Food and Drug Administration (FDA) granted breakthrough therapy designation for lecanemab in AD.[5]

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.[6] 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, such as: confusion, disorientation and getting lost in familiar places; difficulty planning or making decisions; problems with speech and language; problems moving around without assistance or performing self-care tasks; personality changes, such as becoming aggressive,

[a] Information provided by the Eisai Ltd

demanding and suspicious of others; hallucinations (seeing or hearing things that are not there) and delusions (believing things that are untrue); low mood or anxiety.[7]

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.[7] The 2020-2021 Hospital Episode Statistics (HES) for England recorded a total of 2,628 finished consultant episodes (FCE) for dementia in AD (ICD-10 code: F00), resulting in 1,425 hospital admissions, 73,220 FCE bed days and 25 day cases.[8] 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.[9]

Recommended Treatment Options

There is currently no cure for AD, but there are medicinal products available that can temporarily reduce the symptoms. National Institute for Health and Care Excellence (NICE) recommends:[7,10]

- Acetylcholinesterase (AChE) inhibitors (donepezil, galantamine and rivastigmine). These medicinal products increase levels of acetylcholine, a substance in the brain that helps nerve cells communicate with each other.
- Memantine. This medicinal product is not an AChE inhibitor. It works by blocking the effects of an excessive amount of a chemical in the brain called glutamate. Memantine is used for moderate or severe AD. It is suitable for those who cannot take or are unable to tolerate AChE inhibitors.

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.[7]

Clinical Trial Information

Trial	NCT03887455; EudraCT 2018-004739-58; A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease **Phase III** - active, not recruiting **Location(s):** Five EU countries, UK, USA, Canada and other countries **Primary completion date:** September 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N=1,766 (estimated enrolment); Subjects diagnosed with mild cognitive impairment (MCI) due to AD or mild AD dementia
Intervention(s)	Lecanemab 10 mg/kg bi-weekly IV infusion
Comparator(s)	Placebo bi-weekly IV infusion
Outcome(s)	• Core Study: Change from Baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at 18 Months [Time frame: Baseline, 18 months] • Extension Phase Incidence of adverse events (AEs) and changes in vital signs, electrocardiogram values, laboratory safety tests, suicidality

	assessments, antidrug antibodies, and magnetic resonance imaging (MRI) safety parameters • Extension Phase: Change from Core Study Baseline in CDR-SB [Time Frame: Baseline up to Month 45] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT01767311, EudraCT 2012-002843-11; A Placebo-Controlled, Double-Blind, Parallel-Group, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study With an Open-Label Extension Phase to Evaluate Safety, Tolerability and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease **Phase II** – active, not recruiting **Location(s):** Six EU countries, UK, USA, Canada, Japan and Republic of Korea **Primary study completion date:** March 2022
Trial Design	Randomised, parallel assignment, triple-blinded
Population	N=856; Subjects with mild cognitive impairment due to AD or mild AD dementia
Intervention(s)	Lecanemab 2.5 mg/kg, 5.0 mg/kg or 10 mg/kg bi-weekly or 5.0 mg/kg or 10 mg/kg monthly, IV infusion
Comparator(s)	Matched placebo
Outcome(s)	• Core Study: Change from Baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months [Time frame: Baseline and 12 months] • Core Study and Extension Phase: Safety will be assessed by monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) [Time frame: From the time the participant signs the informed consent form until 3 months after the last dose of study drug or through the last visit, whichever is longer; up to 78 months] See trial record for full list of other outcomes.
Results (efficacy)	At 12 months, the 10-mg/kg bi-weekly effective dose 90% (ED90) showed a 64% probability to be better than placebo by 25% on ADCOMS, which missed the 80% threshold for the primary outcome. At 18 months, 10-mg/kg bi-weekly lecanemab reduced brain amyloid (−0.306 Standard Uptake Value ratio (SUVr) units) while showing a drug-placebo difference in favour of active treatment by 27% and 30% on ADCOMS, 56% and 47% on Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14), and 33% and 26% on Clinical Dementia Rating-Sum-of-Boxes (CDR-SB) versus placebo according to Bayesian and frequentist analyses, respectively. CSF biomarkers were supportive of a treatment effect.[4]

Results (safety)	Lecanemab was well-tolerated with 9.9% incidence of amyloid-related imaging abnormalities-edema/effusion at 10 mg/kg bi-weekly.[4]

Estimated Cost

The cost of Lecanemab 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 (TA10739). Expected May 2022.
- NICE technology appraisal. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (TA217). March 2011.
- 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.[11]
- British Columbia Medical Journal. Cognitive Impairment Guideline. 2015.[12]
- European Journal of Neurology. EFNS guidelines for the diagnosis and management of Alzheimer's disease. 2010.[13]

Additional Information

References

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