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HEALTH TECHNOLOGY BRIEFING
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Aducanumab for mild cognitive impairment due to Alzheimer's disease

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Developer/Company	Biogen	**UKPS ID**	647010

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Aducanumab is currently in clinical development for the treatment of mild cognitive impairment due to Alzheimer's disease. Alzheimer's disease 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 Alzheimer's disease 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 Alzheimer's disease are aimed at relieving the symptoms (including cognitive impairment) rather than stopping the progression of the disease.

Aducanumab is a highly selective human antibody that specifically targets the β-amyloid (Aβ) protein which builds up in abnormal levels in the brain of people with Alzheimer's disease. High levels of Aβ result in the protein clumping together to form plaques which disrupt neurone function. Aducanumab is given through intravenous infusion and if licensed, would offer an additional treatment option for Alzheimer's disease and the first to treat the underlying disease rather than the symptoms.

PROPOSED INDICATION

Treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD.[a]

TECHNOLOGY

DESCRIPTION

Aducanumab (BIIB037) is a high affinity, fully human IgG_{1K} monoclonal antibody targeting a conformational epitope found on β-amyloid (Aβ).[1,2] It is derived from a de-identified library of B cells collected from healthy elderly subjects with no sign of cognitive impairment and cognitively impaired elderly subjects with unusually slow cognitive decline.[2] The rationale being that these donors' immune systems had successfully resisted AD and that the operative antibodies could be turned into therapeutics by a process called reverse translational medicine.[1] The precise mechanism by which aducanumab exerts its therapeutic effects in AD is unknown but is presumed to involve targeting aggregated forms of Aβ, including soluble oligomers and insoluble fibrils deposited into the amyloid plaque in the brain of AD patients.[2]

Aducanumab is currently in clinical development for the treatment of MCI due to AD and mild AD. In the phase III clinical trials EMERGE (NCT02484547, EudraCT 2015-000967-15)[3,4] and ENGAGE (NCT02477800, EudraCT 2015-000966-72)[5,6]patients are given monthly intravenous infusions of either a low dose or high dose aducanumab.

INNOVATION AND/OR ADVANTAGES

Currently there is no cure for AD. Medications that are currently available are designed to temporarily reduce the symptoms of AD but do not slow down the progression of the underlying disease.[7]

Results from the phase I PRIME study show that in patients with mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose and time dependent manner.[2,8] This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes (CDR-SB) and Mini Mental State Examination scores (MMSE). [8]

Results from phase III EMERGE study show that at 78 weeks there was a statistically significant slowing in clinical decline as measured by CDR-SB, MMSE, Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 item (ADAS-Cog 13) AND Alzheimer's Disease Cooperative Study – Activities of Daily Living mild cognitive impairment version (ADCS-ADL-MCI). PET scans also showed a reduction in brain amyloid levels.[9]

If licensed Aducanumab would be the first authorised disease modifying treatment that reduces the clinical decline of AD.[10]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

[a] Information provided Biogen on UK PharmaScan

Aducanumab was granted a PRIME designation by the EMA in June 2016, however this was withdrawn in 2019 following the discontinuation of the on-going clinical studies.[11]

Aducanumab was given a fast track designation by the FDA in September 2016.[12]

PATIENT GROUP

DISEASE BACKGROUND

Alzheimer's disease (AD) is a neurodegenerative disease and is the most common type of dementia accounting for 60-70% of dementia cases.[13] It develops gradually over many years and symptoms become more severe. The first sign of AD is usually minor memory problems such as forgetting recent conversations or events and forgetting the names of places or objects.[14] A healthy brain transmits electrical and chemical signals between billions of neurones to send messages between different parts of the brain and from the brain to other parts of the body. AD disrupts communication among neurones, resulting in loss of function and cell death. Initially, AD typically destroys neurons and their connections in parts of the brain involved in memory such as the entorhinal cortex and hippocampus.[15]

The two core pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles. The amyloid cascade hypothesis states that Aβ related toxicity is the primary cause of synaptic dysfunction and subsequent neurodegeneration that underlies the progression characteristics of AD.[8] The plaques interfere with synaptic activity and initiate a series of downstream effects, including formation of neurofibrillary tangles, that cause increasing inter and intra-neuronal dysfunction and ultimately cell death.[16,17] Although it is still unknown exactly what triggers Alzheimer's disease, several factors such as age, family history, down's syndrome, head injuries, cardiovascular disease and having the ε4 form of the APOE gene are known to increase a person's risk of developing the condition.[18,19]

Mild cognitive impairment (MCI) due to AD refers to the symptomatic pre-dementia phase of AD.[9] The term MCI describes a set of symptoms rather than a specific disease. A person with MCI has mild problems with one or more of the following: memory, reasoning, attention, language, or visual depth perception.[19] The changes are serious enough to be noticed by the person affected and to their family members and friends but, unlike dementia, do not significantly affect the individual's ability to carry out everyday activities.[20,21]

CLINICAL NEED AND BURDEN OF DISEASE

Alzheimer's disease and other dementias are a leading cause of death in the UK.[22] In England and Wales in 2018 there were 541,589 deaths where Dementia was registered as the underlying cause, this equated to 12.8% of all registered deaths.[23] Currently 850,000 people are estimated to be living with dementia in the UK. This is expected to rise to 1,142,677 by 2025.[24] An estimated 60-70% of dementia cases will be AD dementia.[13]

In England, in 2018/19 there were 11,062 finished consultant episodes (FCE) for AD (ICD-10 code: G30), resulting in 4,847 admissions, and 230,953 FCE bed days.[25]

The prevalence of MCI in adults aged over 65 years is 10-20%, risk increases with age and men appear to be at a higher risk than women.[26] However, not all patients with MCI will go on to develop dementia, including Alzheimer's dementia. In research studies carried out in memory clinics, <5-20%

of people who had MCI with gradual memory loss went on to develop dementia – usually AD – each year.[19,26] In MCI subjects positive for AD biomarkers, the three-year progression rate to AD-type dementia was 59% compared to only 4% in subjects with no abnormal AD biomarkers.[27]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no therapeutic cure for AD, medications aim to temporarily reduce the symptoms. Treatment may also involves therapies and activities that include cognitive stimulation therapy, cognitive rehabilitation and reminiscence and life story work. Support is also available to help someone with the condition, and their family, cope with everyday life.[28]

Current NICE guidelines provides a range of recommendations including assessment and diagnosis, involving people living with dementia in decisions about their care, interventions to promote cognition, independence and wellbeing, managing non-cognitive symptoms and supporting carers.[29]

CURRENT TREATMENT OPTIONS

Medication available that can temporarily reduce the symptoms of AD:[28,29]

- Acetylcholinesterase (ACE) inhibitors: donepezil, galantamine and rivastigmine (mild to moderate AD)
- Memantine (moderate or severe AD)

NICE guidelines provide specific conditions under which these treatments options should be used for managing mild, moderate and severe AD.[29]

PLACE OF TECHNOLOGY

If licensed, aducanumab will offer a new treatment option for patients with MCI due to AD and mild AD and may potentially be the first treatment option to impact the underlying disease pathology and slow the decline in clinical outcomes.

CLINICAL TRIAL INFORMATION

Trial	**EMERGE**, NCT02484547, EudraCT 2015-000967-15; A Phase 3 Multicenter, Randomized, Double-blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease **Phase III - Terminated** **Locations: 9 EU** (not incl UK), USA, Canada and other countries.
Trial design	Randomized, parallel assignment, double-blind, placebo-controlled study
Population	N=1638; aged 50 to 85 years; clinical dementia rating global score of 0.5; objective evidence of cognitive impairment at screening; mini-mental state exam (MMSE) between 24 and 30
Intervention(s)	Low dose or high dose aducanumab (intravenous infusion)

Comparator(s)	Placebo
Outcome(s)	Change from baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score [Time Frame: Week 78] See trial record for full list of other outcomes
Results (efficacy)	In the high dose group there was a statistically significant reduction in clinical decline as measured by each of these scores: 22% reduction in decline as measured by the CDR-SB score, 18% reduction in decline as measured by the MMSE, a 27% reduction in decline as measured by The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog 13) and a 40% reduction in decline as measured by Alzheimer's Disease Cooperative Study/Activities of Daily Living adapted for MCI patients (ADCS-ADL-MCI) score. PET scans also revealed reduced brain amyloid levels.[30,31]
Results (safety)	Patients with serious adverse events (SAE) was similar across the placebo, low dose and high dose groups; 14.1%, 12.7% and 12.1% respectively. 2.9% of patients permanently discontinued due to adverse events in the placebo group, 7.7% in the low dose group and 8.8% in the high dose group. The most common adverse events in the placebo, low dose and high dose groups were Amyloid-related imaging abnormalities (ARIA)-E (2.2%, 25.7% and 34.0%), headache (15.2%, 19.5% and 19.4%), microhaemorrhage (6.9%, 16.2% and 18.6%), nasopharyngitis (16.5%, 12.9% and 15.9%), superficial siderosis (2.6%, 9.2% and 13.3%) and fall (12.4%, 11.8% and 12.6%).[31]

Trial	**ENGAGE**, NCT02477800, EudraCT 2015-000966-72; A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease **Phase III - Terminated** **Locations**: 8 EU countries (incl UK) USA, Canada and other countries
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled study
Population	N=1647; clinical dementia (CDR) global score of 0.5; objective evidence of cognitive impairment at screening; mini-mental state exam (MMSE) between 24 and 30
Intervention(s)	Low dose or high dose aducanumab (intravenous infusion)
Comparator(s)	Placebo
Outcome(s)	Change from baseline in CDR-SB score [Time Frame: Week 78] See trial record for full list of other outcomes
Results (efficacy)	No obvious benefit of aducanumab over placebo when analysing the final cognitive test datasets from all participants who had completed 78 weeks on trial.[30] In a post hoc analysis, in patients enrolled after a dose-changing amendment permitting all patients to receive 10 mg/kg aducanumab; in patients who had the opportunity to receive 14 doses of 10 mg/kg there was a 27% reduction in clinical decline compared to placebo as measured by CDR-SB.[31]

Results (safety)	Patients with serious adverse events was similar across the placebo, low dose and high dose groups; 12.8%, 13.0% and 12.7% respectively. 5.2% of patients discontinued due to adverse events in the placebo group, 8.2% in the low dose group and 11.5% in the high dose group. The most common adverse events in the placebo, low dose and high dose groups were Amyloid-related imaging abnormalities (ARIA)-E (3.0%, 25.4% and 35.5%), headache (15.0%, 17.9% and 20.4%), microhaemorrhage (5.7%, 15.5% and 17.6%), nasopharyngitis (12.4%, 11.7% and 11.8%), superficial siderosis (1.8%, 8.8% and 15.4%) and fall (10.2%, 14.1% and 14.9%).[31]

ESTIMATED COST

The estimated cost of aducanumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. 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.
- British Columbia Medical Journal. Cognitive Impairment Guideline. 2015.
- European Journal of Neurology. EFNS guidelines for the diagnosis and management of Alzheimer's disease. 2010.[32]
- National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease
- International Working Group (IWG-2) Diagnostic Criteria for Alzheimer's Disease

ADDITIONAL INFORMATION

REFERENCES

1 ALZFORUM. *Adacanumab.* 2020. Available from: https://www.alzforum.org/therapeutics/aducanumab [Accessed 18 February 2020].

2 Creative Biolabs. *Aducanumab Overview.* 2020. Available from: https://www.creativebiolabs.net/aducanumab-overview.htm [Accessed 17 February 2020].

3 Clinicaltrials.gov. *221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease*. *Trial ID:* Status: Terminated. Available from: https://ClinicalTrials.gov/show/NCT02484547 [Accessed 20 February 2020].

4 EU Clinical Trials Register. *A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease*. *Trial ID: 2015-000967-15*. 2015. Status: Completed. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000967-15/DE/ [Accessed 20 February 2020].

5 Clinicaltrials.gov. *221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease*. *Trial ID:* Status: Terminated. Available from: https://ClinicalTrials.gov/show/NCT02477800 [Accessed 20 February 2020].

6 EU Clinical Trials Register. *A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease*. *Trial ID: 2015-000966-72*. 2016. Status: Completed. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000966-72/GB/ [Accessed 20/02/2020].

7 Alzheimer's Society. *Drug treatments For Alzheimer's disease.* 2020. Available from: https://www.alzheimers.org.uk/about-dementia/treatments/drugs/drug-treatments-alzheimers-disease [Accessed 18 February 2020].

8 Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*. 2016 2016/09/01;537(7618):50-6. Available from: https://doi.org/10.1038/nature19323.

9 Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011;7(3):270-9. Available from: https://doi.org/10.1016/j.jalz.2011.03.008.

10 Biogen. *Biogen plans regulatory filing for aducanumab in alzheimers disease based on new analysis of larger dataset from phase 3 studies.* 2019. Available from: https://investors.biogen.com/news-releases/news-release-details/biogen-plans-regulatory-filing-aducanumab-alzheimers-disease [Accessed 18 February 2020].

11 Biogen. *Biogen's investigational Alzheimers disease treatment aducanumab accepted into european medicines agancy prime program.* 2016. Available from: https://investors.biogen.com/news-releases/news-release-details/biogens-investigational-alzheimers-disease-treatment-0 [Accessed 18 February 2020].

12 Biogen. *Biogens investigational Alzheimers disease treatment aducanumab granted FDA fast track designation.* 2020. Available from: https://investors.biogen.com/news-releases/news-release-details/biogens-investigational-alzheimers-disease-treatment-aducanumab [Accessed 18 February 2020].

13 EU Joint Programme - Neurodegenerative Disease Research. *What is a neurodegenerative disease.* 2020. Available from: https://www.neurodegenerationresearch.eu/what/ [Accessed 24 February 2020].

14 National Health Service (NHS). *Alzheimer's disease: Overview.* 2018. Available from: https://www.nhs.uk/conditions/alzheimers-disease/ [Accessed 12 February 2020].

15 National Institute on Aging. *What happens to the Brain in Alzheimers Disease?* 2017. Available from: https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease [Accessed 12 February 2020].

16 Cleveland Clinic. *Alzheimer's Disease.* 2017. Available from: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/alzheimers-disease/ [Accessed 12 February 2020].

17 Barage SH, Sonawane KD. Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. *Neuropeptides*. 2015 2015/08/01/;52:1-18. Available from: https://doi.org/https://doi.org/10.1016/j.npep.2015.06.008.

18 National Health Service (NHS). *Alzheimer's Disease: Causes.* 2018. Available from: https://www.nhs.uk/conditions/alzheimers-disease/causes/ [Accessed 12 February 2020].
19 Alzheimer's society. *What is mild cognitive impairment (MCI)?* 2015. Available from: https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_what_is_mild_cognitive_impairment_mci.pdf [Accessed 20 Februrary 2020].
20 Alzheimers Association. *Mild Cognitive Impairment (MCI).* 2020. Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment [Accessed 12 February 2020].
21 Alzheimers Research UK. *Mild Cognitive Impairment.* 2020. Available from: https://www.alzheimersresearchuk.org/about-dementia/types-of-dementia/mild-cognitive-impairment/about/ [Accessed 12 February 2020].
22 Alzheimers Research UK. *Deaths due to Dementia.* 2018. Available from: https://www.dementiastatistics.org/statistics/deaths-due-to-dementia/ [Accessed 04 March 2020].
23 The Guardian. *Alzheimer's and dementia leading cause of death in England and Wales.* 2019. Available from: https://www.theguardian.com/society/2019/aug/06/alzheimers-dementia-leading-cause-death-england-wales [Accessed 04 March 2020].
24 Alzheimers Research UK. *Dementia Prevalence.* 2020. Available from: https://www.dementiastatistics.org/statistics-about-dementia/prevalence/ [Accessed 04 March 2020].
25 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Downloaded 19 September 2019].
26 Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA*. 2014;312(23):2551-61. Available from: https://doi.org/10.1001/jama.2014.13806.
27 Vos SJB, Verhey F, Frölich L, Kornhuber J, Wiltfang J, Maier W, et al. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain : a journal of neurology*. 2015;138(Pt 5):1327-38. Available from: https://doi.org/10.1093/brain/awv029.
28 National Health Service (NHS). *Alzheimer's disease: Treatment.* 2018. Available from: https://www.nhs.uk/conditions/alzheimers-disease/treatment/ [Accessed 20 February 2020].
29 National Institute for Health and Care Excellence (NICE). *Dementia Management.* 2020. Available from: https://pathways.nice.org.uk/pathways/dementia#path=view%3A/pathways/dementia/dementia-management.xml&content=view-node%3Anodes-pharmacological-interventions [Accessed 24/02/2020].
30 Alhzeimer Europe. *Biogen announces topline results from the EMERGE and ENGAGE Phase III clinical trials of Aducanumab.* 2019. Available from: https://www.alzheimer-europe.org/News/Science-watch/Thursday-05-December-2019-Biogen-announces-topline-results-from-the-EMERGE-and-ENGAGE-Phase-III-clinical-trials-of-Aducanumab [Accessed 20 February 2020].
31 Biogen. *EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients with Early Alzheimer's Disease.* 2019. Available from: https://investors.biogen.com/static-files/ddd45672-9c7e-4c99-8a06-3b557697c06f [Accessed 20 February 2020].
32 Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *European Journal of Neurology*. 2010 2010/10/01;17(10):1236-48. Available from: https://doi.org/10.1111/j.1468-1331.2010.03040.x.

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