Health Technology Briefing
May 2022

Gantenerumab for Alzheimer's disease

Company/Developer	Roche Products Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 5825	NICE ID: 10668	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Gantenerumab 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, the cells that carry signals or information messages to and from the brain and the rest of the body. 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.

Gantenerumab is a monoclonal antibody (a type of protein) that preferentially attaches to-amyloid (Aβ) plaques which are associated with the development of AD. Gantenerumab reduces small plaques by recruiting microglia the brains defence cells and prevents the formation of new plaques. Gantenerumab is administered subcutaneously and if licensed, would offer an additional treatment option for adults with early AD, and a novel treatment option to modify the underlying disease process rather than treating the symptoms of the disease.

Proposed Indication

For the treatment of adults with early (prodromal to mild) Alzheimer's disease (AD).[1-5]

Technology

Description

Gantenerumab (R-1450) is a fully human IgG1 antibody that binds with sub-nanomolar affinity to a conformational epitope on beta-amyloid (Aβ) fibrils. It includes both N-terminal and central amino acids that are spatially juxtaposed in Aβ oligomers and fibrils.[6] In vitro studies have revealed gantenerumab preferentially interacts with aggregated Aβ in the brain and lowers Aβ by eliciting effector cell-mediated clearance.[7] Gantenerumab works centrally to disassemble and degrade amyloid plaques by recruiting microglia and activating phagocytosis. This antibody interacts with aggregated brain Aβ, both vascular and parenchymal. Gantenerumab elicits phagocytosis of human Aβ deposits in AD brain slices co-cultured with human macrophages. It is also known to bind to cerebral Aβ, reduces small plaques by recruiting microglia, and prevents new plaque formation in APP/PS-1 transgenic mice.[8] Gantenerumab removes amyloid-β plaques through the Fcγ receptor mediated phagocytosis and counteracts the neurotoxic effect of oligomeric amyloid-β_{42} in vivo.[9]

Gantenerumab is currently in phase II/III (NCT01760005) and phase III (NCT03444870; NCT03443973; NCT01224106; NCT02051608) clinical development for the treatment of adults with prodromal to mild AD. In these trials, gantenerumab is administered subcutaneously.[1-5] There is also a phase III GRADUATION study (NCT04592341) to evaluate once weekly administration, after initial dose titration. In this study, gantenerumab is administered subcutaneously, with a dose escalation of 120mg to 255mg.[10]

Key Innovation

Gantenerumab is a novel, fully human anti-Aβ antibody that has been optimised for binding to conformational epitopes expressed on amyloid-β fibrils. It is hypothesised that this high affinity binding, and recruitment of brain effector cells is required for the most efficient amyloid clearance. In transgenic mice studies, long-term treatment with gantenerumab has been shown to significantly decrease the amyloid plaque load. Similarly, a dose-dependent amyloid reduction was observed in the brains of patients with AD following 2 to 7 months of gantenerumab treatment.[7,11]

A combination of in vivo and in vitro studies, have shown the requirement for effector cells, signifying the removal of Aβ plaque by gantenerumab is primarily mediated by phagocytosis and intracellular degradation.[7,11] If licensed, gantenerumab will be a novel technology that modifies the underlying pathophysiology of AD by reducing the Aβ plaque and prevents new plaque formation.[9]

Regulatory & Development Status

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

Gantenerumab has a Breakthrough Therapy by the US FDA for AD in October 2021.[8,12]

Gantenerumab is not currently in phase II or III development for any other indications.[13]

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 whereby abnormal levels of Aβ protein clump together to form amyloid plaques. These amyloid plaques aggregate between the neurones in the brain and disrupt cell function.[14,15] 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, 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.[16]

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.[16] Of 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 (105.5 per 100,000) compared with females (120.4 per 100,000).[17] 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.[18]

Recommended Treatment Options

There is currently no cure for AD, but there are medicinal products available that can temporarily reduce the symptoms.[16] In patients with mild-to-moderate AD, National Institute for Health and Care Excellence (NICE) recommends acetylcholinesterase (AChE) inhibitors (donepezil hydrochloride, galantamine and rivastigmine).[19]

Clinical Trial Information

Trial	NCT03444870; 2017-001364-38; A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) Alzheimer's Disease **Phase III** – Recruiting **Locations:** 6 EU countries, USA, Canada, and other countries **Primary completion date:** September 2022
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=1016 (estimated); subjects with probable AD dementia or prodromal AD; aged 50 to 90 years old
Intervention(s)	Gantenerumab administered as subcutaneous injections with gradual uptitration.

Comparator(s)	Placebo administered as subcutaneous injections with gradual uptitration
Outcome(s)	Primary outcome: Change from baseline to week 116 in global outcome, as measured by clinical dementia rating-sum of boxes (CDR-SOB) [Time Frame: Baseline Up to Week 116] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT03443973; 2017-001365-24; A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) Alzheimer's Disease **Phase III** – Active, Not recruiting **Locations:** 9 EU countries, UK, USA and other countries **Primary completion date:** September 2022
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=982 (actual); Subjects diagnosed with probable AD dementia or prodromal AD; aged 50 to 90 years old
Intervention(s)	Gantenerumab administered as subcutaneous injections with gradual uptitration.
Comparator(s)	Placebo administered as subcutaneous injections with gradual uptitration
Outcome(s)	Primary outcome: Change from baseline to week 116 in global outcome, as measured by CDR-SOB [Time Frame: Baseline up to Week 116] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT01760005; A Phase II/III Randomized, Double-Blind, Placebo-Controlled, Cognitive Endpoint, Multi-Center Study of Potential Disease Modifying Therapies in Individuals at Risk for and With Dominantly Inherited Alzheimer's Disease **Phase II/III** – Recruiting **Locations:** 6 EU countries, UK, USA, Canada and other countries **Primary completion date:** July 2022
Trial Design	Randomised, quadruple-masked, double-blind, placebo-controlled, parallel assignment
Population	N=490 (estimated); Subjects who know they have an AD causing mutation or are unaware of their genetic status and have dominantly inherited Alzheimer's

	disease (DIAD) mutation in their family; are cognitively normal or with mild cognitive impairment or mild dementia; aged 18 to 80 years old
Intervention(s)	Gantenerumab administered as subcutaneous injections every 4 weeks at escalating doses
Comparator(s)	Matching placebo administered subcutaneously every 4 weeks
Outcome(s)	Primary outcome: Assess cognitive efficacy in individuals with mutations causing dominantly inherited AD as measured by the change from baseline in the DIAN-Multivariate cognitive endpoint (DIAN-MCE) [Time Frame: Baseline and Weeks 52, 104, 156, and 208]
Results (efficacy)	-
Results (safety)	-

Trial	**SCARLET ROAD**; NCT01224106; 2010-019895-66; Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Two Year Study to Evaluate the Effect of Subcutaneous RO4909832 on Cognition and Function in Prodromal Alzheimer's Disease With Option for up to an Additional Two Years of Treatment and an Open-Label Extension With Active Study Treatment **Phase III –** Completed **Locations:** 10 EU countries, UK, USA, Canada, and other countries **Primary completion date:** September 2020
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=799; Subjects with prodromal AD who are not receiving memantine or cholinesterase inhibitors; aged 50 to 85 years old
Intervention(s)	Gantenerumab at 105 mg, 225 mg, or at doses up to 1200 mg administered by subcutaneous injections every 4 weeks (Q4W) for 104 weeks or approximately 2 years
Comparator(s)	Matching placebo administered (subcutaneous injection)
Outcome(s)	Primary outcome: • Mean change from baseline CDR-SOB total score at week 104 (double-blind treatment phase) [Time Frame: Baseline, Week 104] • Number of participants with adverse events (AEs) or serious adverse events (SAEs) (Open label extension phase) [Time Frame: Baseline up until a maximum of 5 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02051608; 2013-003390-95; A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Efficacy and Safety Study of Gantenerumab in Patients With Mild Alzheimer's Disease; Part II: Open-Label Extension For Participating Patients **Phase III –** Completed **Locations:** 13 EU countries, UK, USA, Canada and other countries **Primary completion date:** April 2021
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled, parallel group
Population	N=389; Clinical diagnosis of probable mild AD; aged 50 to 90 years old
Intervention(s)	Gantenerumab administered as subcutaneous injections every 4 weeks
Comparator(s)	Matching placebo administered subcutaneously every 4 weeks
Outcome(s)	Primary outcomes: • Mean Change From Baseline in Alzheimer's Disease Activity Scale-Cognitive subscale 13 (ADAS-Cog13) scores at Week 104 [Time Frame: Baseline, Week 104] • Mean Change From Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scores at week 104 [Time Frame: Baseline, Week 104] • Percentage of Participants with Adverse Events (AEs) or Serious Adverse Events (SAEs) [Time Frame: Baseline up to approximately 7 years]
Results (efficacy)	Gantenerumab doses up to 1200 mg resulted in robust amyloid-β plaque removal at 2 years. PET amyloid levels were consistent with sparse-to-no neuritic amyloid-β plaques in 51% of patients after 2 years of therapy.[9]
Results (safety)	-

Trial	NCT04592341; 2020-001384-87; A Phase II, Multicenter, Open-Label, Single Arm Study to Evaluate the Pharmacodynamic Effects of Once Weekly Administration of Gantenerumab in Participants With Early (Prodromal to Mild) Alzheimer's Disease **Phase III –** Active, not recruiting **Locations:** 6 EU countries, UK, USA **Primary completion date:** July 2023
Trial Design	Sequential, open label
Population	N=193; Clinical diagnosis of Alzheimer's Disease (AD) dementia or prodromal AD; aged 50 to 90 years old
Intervention(s)	Gantenerumab administered as subcutaneous (SC) injection at a dose of 120 mg every 4 weeks (Q4W) for 12 weeks, followed by 255 mg Q4W for 12 weeks, and 255 mg every 2 weeks (Q2W) for another 12 weeks, followed by the target dose 255 mg once weekly (Q1W) for up to Week 103
Comparator(s)	No comparator

Outcome(s)	Primary outcomes: Change from Baseline in Deposited Amyloid as Measured by Brain Amyloid PET Centiloid (CL) Levels [Time Frame: Up to Week 104] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of gantenerumab 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 date of issue to be confirmed.
- 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.[20]
- British Columbia Medical Journal. Cognitive Impairment Guideline. 2015.[21]
- National Institute on Aging. Alzheimer's Disease Diagnostic Guidelines. 2011.[22]
- European Journal of Neurology. EFNS guidelines for the diagnosis and management of Alzheimer's disease. 2010.[23]

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