SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Kisunla 350 mg concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 350 mg donanemab in 20 ml (17.5 mg/ml)

Donanemab is a humanised monoclonal antibody (IgG1) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect

Each 20 ml vial contains 11.5 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The solution is clear to opalescent, colourless to slightly yellow to slightly brown with a pH of 5.5 – 6.5 and osmolarity of approximately 300 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Donanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (AD) in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the diagnosis and treatment of Alzheimer's disease. The infusion of donanemab should be initiated and supervised by an experienced healthcare professional capable of detecting and managing infusion related reactions who has access to appropriate medical support to manage severe reactions (see section 4.4).

Beta amyloid evidence

Beta amyloid evidence consistent with AD should be confirmed using a validated test such as amyloid Positron Emission Tomography (PET) scan or cerebrospinal fluid (CSF) analysis or equivalent validated methods, prior to initiating treatment (see section 5.1).

Testing for apolipoprotein E ε4 (ApoE ε4) status should be performed prior to initiation of treatment (see section 4.1). Prior to testing patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

Posology

The recommended dose of donanemab is 700 mg every 4 weeks for the first 3 doses, followed by 1400 mg every 4 weeks. Treatment should be continued until amyloid plaques are cleared as confirmed using a validated method up to a maximum of 18 months (see section 5.1).

Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible (see section 5.1).

The duration of placebo-controlled efficacy data for donanemab is limited to 18 months (see section 5.1).

The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis.

If patient progress to moderate Alzheimer's disease before the end of the 18 months maximum treatment, donanemab should be stopped.

Monitoring for Amyloid Related Imaging Abnormalities (ARIA)

Donanemab can cause amyloid related imaging abnormalities-oedema (ARIA-E) and -haemosiderin deposition (ARIA-H), see section 4.4.

Access to MRI should be available during the treatment period of donanemab.

Obtain a recent (within 1 year) brain magnetic resonance imaging (MRI) prior to initiating treatment. Perform an MRI prior to the second dose, prior to dose increase, and prior to the seventh dose (see section 4.4).

For patients with radiographic findings of ARIA-E and ARIA-H, enhanced clinical vigilance for symptoms of ARIA is recommended. Additional MRIs may be considered, if clinically indicated (see section 4.4).

The recommendations for dosing interruptions or treatment discontinuation for patients with amyloid-related imaging abnormalities-oedema/effusions (ARIA-E) and amyloid-related imaging abnormalities haemorrhage/haemosiderin deposition (ARIA-H) are provided in Table 1.

Table 1: Dosing recommendations for patients with ARIA-E and ARIA-H

Clinical Symptom	**ARIA-E and ARIA-H Severity[a] on MRI**		
	Mild	**Moderate**	**Severe**
Asymptomatic	Consider suspending dosing	Suspend dosing	Suspend dosing
Symptomatic	Suspend dosing		

[a]See Table 2 for ARIA MRI radiographic severity classification

Evaluation of risk factors again prior to restarting is recommended. Supportive treatment, including corticosteroids may be considered in case of ARIA-E.

ARIA-E

Dosing may continue in asymptomatic, mild radiographic ARIA-E cases based on clinical judgement and with enhanced clinical monitoring and follow-up MRI scans starting two months after occurrence and every 1 or 2 months thereafter until ARIA-E has resolved.

Suspend dosing for any symptomatic or radiographically moderate or severe ARIA-E. A follow-up MRI to assess for resolution 2 to 4 months after initial identification should be performed. Once the MRI demonstrates radiographic resolution and symptoms (see section 4.4), if present, resolve, resumption of dosing should be guided by clinical judgment.

Following an initial event of ARIA-E, the rate of recurrence on resumption of treatment with donanemab is very common (see section 4.8).

ARIA-H

Dosing may continue in asymptomatic, mild radiographic ARIA-H cases based on clinical judgement and with enhanced clinical monitoring and follow-up MRI scans starting two months after occurrence and every 1 or 2 months thereafter until ARIA-H has stabilised.

Suspend dosing for any symptomatic or radiographically moderate or severe ARIA-H. A follow-up MRI to assess for resolution 2 to 4 months after initial identification should be performed. Once the MRI demonstrates radiographic stabilisation and symptoms (see section 4.4), if present, resolve, resumption of dosing should be guided by clinical judgment.

Following an initial event of ARIA-H, the rate of recurrence on resumption of treatment with donanemab is very common (see section 4.8).

If a second event of radiographically severe ARIA-H occurs, use clinical judgement in considering whether to restart or permanently discontinue treatment with donanemab.

Intracerebral haemorrhage

In patients who develop intracerebral haemorrhage greater than 1 cm in diameter during treatment with donanemab, dosing should be permanently discontinued (see sections 4.3 and 4.4).

Method of administration

Kisunla 350 mg is for intravenous infusion only. Each vial is for single use only. It should be administered over at least 30 minutes. Patients should be observed post-infusion for a minimum of 30 minutes. For instructions on dilution of the medicinal product before administration, see section 6.6.

The vial should be inspected visually for particulate matter and discolouration prior to administration. Do not use donanemab if it is cloudy or there are visible particles.

Missed dose

If an infusion is missed, the missed dose should be administered at the next possible occasion. Then, resume the recommended dosing regimen every 4 weeks.

Special populations

Paediatric population

There is no relevant use of Kisunla in the paediatric population for the treatment of Alzheimer's disease.

Elderly

No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

Renal impairment/hepatic impairment

Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal or hepatic impairment (see section 5.2). The effect of severe hepatic and severe renal impairment on the exposure of donanemab has not been studied.

Down's syndrome

The safety and efficacy of donanemab in adults with Down's syndrome has not been established (see section 4.4).

4.3 Contraindications

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Imaging findings suggestive of Cerebral Amyloid Angiopathy (CAA) that increase the risk of ARIA or intracerebral haemorrhage:

- Acute or subacute cerebral haemorrhage
- Superficial siderosis
- More than 4 microhaemorrhages (defined as ≤ 1 cm in diameter on the T2* sequence)
- Severe white matter disease
- Pre-treatment MRI showing ARIA-E
- Previous cerebral haemorrhage (defined as > 1 cm diameter in the T2* sequence) or previous subarachnoid haemorrhage unless it is no longer at risk of re-bleeding.
- Any finding that could prevent a satisfactory MRI evaluation for safety monitoring.

Treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy (see section 4.4).

4.4 Special warnings and precautions for use

Controlled access programme

In order to promote the safe and effective use of donanemab, initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-Related Reactions

Infusion-related reactions, including anaphylaxis have been observed with administration of donanemab (see section 4.8. Undesirable Effects). These reactions may be severe or life-threatening and typically occur during infusion or within 30 minutes post infusion. Signs and symptoms of infusion-related reactions may include erythema, chills, nausea, vomiting, sweating, headache, chest tightness, dyspnoea, and changes in blood pressure. Appropriate resources for the management of severe reactions such as serious IRR, hypersensitivity reactions and/or anaphylactic reactions should be available. Reducing infusion rate, use of premedication or symptomatic treatment may be helpful in managing these reactions.

Administration of donanemab should be discontinued immediately and appropriate treatment should be initiated in case of serious infusion-related reactions or as clinically indicated.

Higher ADA titre was associated with increased incidence of infusion-related reactions.

Amyloid-related imaging abnormalities (ARIA)

ARIA has been observed very commonly in donanemab clinical studies. ARIA usually occurs early in treatment and is usually asymptomatic. Serious cases of ARIA have been observed and some have been fatal (see section 4.8 Undesirable Effects). ARIA includes amyloid-related imaging abnormalities-oedema/effusions (ARIA-E; also known as cerebral vasogenic oedema) and amyloid-related imaging abnormalities haemorrhage/haemosiderin deposition (ARIA-H; includes cerebral microhaemorrhage and cortical superficial siderosis). ARIA can be detected by MRI.

Most ARIA events were first observed within 24 weeks of initiation of treatment. Access to MRI should be available during the treatment period of donanemab.

MRI monitoring

Perform an MRI at baseline (within 1 year to initiating treatment), prior to the second dose, prior to dose increase, and prior to the seventh dose (see section 4.2). Additional MRI is indicated if ARIA symptoms occur. Symptoms may include headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures.

Most serious ARIA events occurred within 12 weeks of initiation of treatment and an additional MRI prior to the third dose may aid in earlier detection of ARIA, particularly for patients with ARIA risk factors such as apolipoprotein E ε4 allele (APOE ε4) carriers, baseline cerebral microhaemorrhages and superficial siderosis.

APOE ε4 carrier status and risk of ARIA

APOE ε4 carriers have a higher frequency (homozygotes greater than heterozygotes) of ARIA-E and ARIA-H compared to non-carriers (see section 4.8). Donanemab is not indicated for use in patients who are ApoE ε4 homozygotes.

A higher frequency of ARIA has also been observed in patients with pre-treatment cerebral microhaemorrhage and/or superficial siderosis.

Caution should be exercised when initiating donanemab treatment in patients with baseline risk factors.

The safety of donanemab has not been established in patients with pre-treatment MRI showing

ARIA-E, more than 4 microhaemorrhages, more than 1 area of superficial siderosis, severe white matter disease or intracerebral haemorrhage greater than 1 cm (see section 4.3).

Intracerebral haemorrhage >1cm

Intracerebral haemorrhage greater than 1 cm in diameter was reported in 0.3% (3/984) of patients after treatment with donanemab compared to 0.2% (2/999) of placebo-treated patients. Fatal events of intracerebral haemorrhage in patients taking donanemab have been observed (see sections 4.2 and 4.3).

Recommendations for Dosing Interruptions in Patients with ARIA

When ARIA-H does occur, it is often in the presence of ARIA-E and managed as for ARIA-E.

The recommendations for dosing interruptions for patients with ARIA-E and ARIA-H are provided in Table 1 (see section 4.2).

Radiographic Severity

The radiographic severity of ARIA associated with donanemab was classified by the criteria shown in Table 2.

Table 2: ARIA MRI Classification criteria

ARIA Type	**Radiographic Severity**		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location < 5 cm.	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring < 10 cm.	FLAIR hyperintensity > 10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H microhaemorrhage	≤ 4 new incident microhaemorrhages	5 - 9 new incident microhaemorrhages	≥ 10 new incident microhaemorrhages
ARIA-H superficial siderosis[a]	1 new focal area of superficial siderosis	2 new focal areas of superficial siderosis	> 2 new focal areas of superficial siderosis

Abbreviations: FLAIR = fluid-attenuated inversion recovery; ARIA-E = amyloid-related imaging abnormalities-oedema/effusions; ARIA-H = amyloid-related imaging abnormalities haemorrhage/hemosiderin deposition

[a] Includes new or increased focal areas of superficial siderosis

Concomitant antithrombotic treatment

The majority of exposures to antithrombotic medicines were to acetylsalicylic acid (81%) and more than 20% were treated with anticoagulants.

Patients who received donanemab and an antithrombotic medicine (acetylsalicylic acid, other antiplatelets, or anticoagulants), did not have an increased frequency of ARIA.

The number of events and the limited exposure to other non-acetylsalicylic acid antithrombotic medicines limit definitive conclusions about the risk of ARIA or intracerebral haemorrhage in patients taking antithrombotic medicines. Because ARIA-H and intracerebral haemorrhages greater than 1 cm in diameter have been observed in patients taking donanemab, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with donanemab.

- If anticoagulation needs to be commenced during therapy with donanemab (for example incident arterial thromboses, acute pulmonary embolism or other life-threatening indications) then donanemab should be paused. Donanemab therapy can be reinstated if anticoagulation is no longer medically indicated. The use of concomitant aspirin and other antiplatelet therapy is permitted.

- There was only limited exposure to thrombolytic agents in the clinical trials however the risk of severe intracranial bleed resulting from concomitant use is plausible. Use of thrombolytic agents should be avoided except for immediately life-threatening indications with no alternative management (e.g., pulmonary embolism with haemodynamic compromise) when the benefits could outweigh the risks.

- Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with donanemab.

Treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy (see section 4.3).

The presence of an ApoE ε4 allele is associated with CAA, which has an increased risk for intracerebral haemorrhage.

Donanemab should not be used in patients with evidence of severe CAA on MRI (see section 4.3). Caution should be exercised when considering the use of donanemab in patients with other factors that indicate an increased risk for intracerebral haemorrhage.

Down's syndrome

There is a higher rate of CAA in patients with Down's syndrome. The safety and efficacy of donanemab in these patients are unknown.

Sodium

This medicinal product contains 46 mg sodium per 1400 mg dose, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No pharmacokinetic drug interactions are expected based on the characteristics of donanemab.

The risk of intracerebral haemorrhage with donanemab treatment is increased in patients receiving anticoagulant therapy or thrombolytic agents (see sections 4.3 and 4.4). Caution should be exercised when considering the administration of antithrombotics because ARIA-H and intracerebral haemorrhages greater than 1 cm in diameter have been observed in patients taking donanemab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of donanemab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Kisunla is not recommended during pregnancy.

Breast-feeding

Lactation studies have not been conducted in animals. Human immunoglobulin G (IgG) is known to be present in human milk; therefore, donanemab may be transmitted from the mother to the breastfed infant. Administer donanemab to nursing women only if the potential benefit outweighs the potential risk for the mother and the infant.

Fertility

There are no data on the effect of donanemab on human fertility. No animal studies have been performed to test donanemab for potential fertility impairment.

4.7 Effects on ability to drive and use machines

Kisunla has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In two placebo-controlled studies (see section 5.1) in patients with AD, a total of 984 adult subjects received at least one dose of donanemab. Of these, 816 participants were in the indicated population.

Based on the ApoE ε4 carrier status, of the patients treated with donanemab, 30 % (291/984) were non-carriers, 53 % (522/984) were heterozygotes and 17 % (168/984) were homozygotes. With the exception of events of ARIA, the safety profile was the same across genotypes.

The most frequently reported adverse reactions in the studied combined population were ARIA-E (24.4 %), ARIA-H (31.3 %) and headache (13.1 %) (see Table 3). The most important serious adverse reactions were: Serious ARIA-E (1.5 %), serious ARIA-H (0.4 %), and serious hypersensitivity including infusion-related reactions (0.6 %). Anaphylaxis was uncommonly reported (0.3 %) (see section 4.4).

In the indicated population, the most common adverse reactions were ARIA-E (20.8 %), ARIA-H (26.7 %) and headache (13.5 %).

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000).

Table 3. Adverse reactions

System organ class	Very common	Common	Uncommon
Immune system disorders			Anaphylaxis
Nervous system disorders	ARIA-E[a] ARIA-H[a, b] Headache		
Gastrointestinal disorders		Nausea	

		Vomiting	
Injury, poisoning and procedural complications		Infusion-related reaction	

[a] As assessed by MRI.

[b] Includes microhaemorrhage and superficial siderosis

Description of selected adverse reactions

Amyloid-related Imaging abnormalities in Indicated Population

ARIA (ARIA-E or ARIA-H) was observed in 32.6 % (266/816) of patients treated with donanemab, compared to 12.7 % (105/825) of patients on placebo in the placebo-controlled studies. Symptomatic ARIA occurred in 5.8 % (47/816) of patients on donanemab. Serious ARIA events were reported in 1.3 % (11/816) of patients treated with donanemab. Clinical symptoms associated with ARIA-E resolved in 75 % (33/44) of patients.

ARIA-E was observed in 20.8 % (170/816) of patients treated with donanemab compared with 1.6 % (13/825) of patients on placebo. The maximum radiographic severity for ARIA-E was mild in 6.5 % of patients, moderate in 12.3 % of patients, and severe in 1.7 % of patients. The majority of ARIA-E was asymptomatic with symptomatic ARIA-E reported for 5.4 % of patients treated with donanemab in placebo-controlled clinical trials. The median time to resolution of ARIA-E was approximately 9 weeks.

ARIA-H can occur spontaneously in patients with AD independent of treatment. ARIA-H was observed in 26.7 % (218/816) of patients treated with donanemab compared with 11.6 % (96/825) of patients on placebo. The maximum radiographic severity for ARIA-H was mild in 14.1 % of patients, moderate in 5.0 % of patients, and severe in 7.5 % of patients. The majority of ARIA-H was asymptomatic with symptomatic ARIA-H reported for 1.0 % (8/816) of patients treated with donanemab compared with 0.2 % (2/825) of patients on placebo. Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 11.8 % (96/816) of donanemab-treated patients compared to 11 % (91/825) on placebo.

The majority of first ARIA radiographic events in the placebo-controlled studies occurred early in treatment (within 24 weeks of initiation of treatment), although ARIA can occur at any time and patients can have more than one episode.

APOE ε4 Carrier Status and Risk of ARIA

In placebo-controlled studies, the incidence of ARIA was lower in non-carriers (24.1 % donanemab vs 11.3 % placebo) and heterozygotes (37.4 % donanemab vs 13.4 % placebo) than in homozygotes (58.3 % donanemab vs 21.3 % placebo). Among patients treated with donanemab, symptomatic ARIA-E occurred in 4.1 % of non-carriers and 6.1 % of heterozygotes compared with 7.7 % of homozygotes. Serious events of ARIA occurred in approximately 0.7 % of non-carriers, 1.7 % heterozygotes and 3% of homozygotes. Among patients treated with donanemab, the

rate of severe radiographic ARIA-E was lower in non-carriers 1.0 % (3/291) and heterozygotes 2.1 % (11/522) compared to homozygotes 4.2 % (7/168). The rate of severe radiographic ARIA-H was lower in non-carriers 4.5 % (13/291) and heterozygotes 9.2 % (48/522) compared to homozygotes 24.4 % (41/168).

Among the patients who experienced an event of ARIA-E and continued on donanemab with or without dose interruption, the rates of recurrence were 32.4 % (11/34) in non-carriers, 26.7 % (27/101) in heterozygotes and 28.6 % (14/49) in homozygotes.

Among the patients who experienced an event of ARIA-H and continued on donanemab with or without dose interruption, the rates of recurrence were 35.1 % (13/37) in non-carriers (compared with 31.8 % [7/22] on placebo), 39.1 % (45/115) in heterozygotes (compared with 38.6 % [17/44] on placebo), and 51.7 % (31/60) in homozygotes (compared with 30.8 % [8/26] on placebo).

Intracerebral Haemorrhage in the Indicated Population

Intracerebral haemorrhage was reported in 0.4 % (3/816) of patients on donanemab compared to 0.2 % (2/825) of patients on placebo.

Infusion-related reactions

Infusion reactions were observed in 8.5 % of patients treated with donanemab compared to 0.4 % on placebo. Anaphylaxis was uncommonly reported (0.3 %). Serious infusion reactions or hypersensitivity occurred in 0.6 % of patients treated with donanemab compared to 0.2 % on placebo. The incidence of infusion-related reactions was similar regardless of ApoE ε4 carrier status.

The majority of infusion reactions and hypersensitivity reactions have occurred within the first 4 doses of donanemab, although they can occur at any time.

Immunogenicity

In clinical studies, 88.1 % of donanemab treated patients developed anti-drug antibodies (ADA) and all of the patients with ADA had neutralising antibodies. Although donanemab exposure decreased with increasing ADA titre, the development of ADA was not associated with loss of clinical efficacy of donanemab. All patients reporting infusion-related reactions had ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single doses up to 40 mg/kg (approximately 2800 mg in a 70 kg person) have been administered.

ARIA-E occurred in 2 out of 4 patients administered this dose and resolved. In case of an overdose, initiate supportive therapy if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, psychoanaleptics, anti-dementia drugs, other anti-dementia drugs, ATC code: N06DX05.

Mechanism of action

Donanemab is an immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble, modified, N-terminal truncated form of amyloid beta (N3pG Aβ) present only in brain amyloid plaques. Donanemab binds to N3pG Aβ and aids plaque removal through microglial-mediated phagocytosis. The accumulation of beta amyloid plaque in the brain is one of the defining pathophysiological features of Alzheimer's disease.

Pharmacodynamic effects

Reductions in cerebral amyloid plaques, as measured by amyloid positron emission tomography (PET), were observed among patients receiving donanemab. Donanemab reduced tau pathophysiology, as measured by plasma P-Tau217.

Clinical efficacy and safety

The safety and efficacy of donanemab were evaluated in a Phase III (TRAILBLAZER-ALZ 2) and a Phase II (TRAILBLAZER-ALZ) study, both double-blind placebo-controlled, parallel-group, in patients with early symptomatic AD (Mild Cognitive Impairment (MCI) or mild dementia due to AD) and evidence of amyloid beta pathology confirmed by amyloid PET scan. The participants also had evidence of pathologic tau deposition on a flortaucipir PET scan. The Phase III study confirmed the efficacy and safety results observed in the Phase II Study. For the safety analysis, patients were followed for up to 76 weeks or last dose plus 57 days.

A small proportion (9.7 %) of patients with history of transient ischemic attacks, stroke or seizures were included in placebo-controlled clinical trials. Although the type and frequency of adverse events were overall comparable to the general study population, there was a slight increased frequency of falls (21% vs 13%) in this subgroup treated with donanemab. However, due to the small number of patients in this subgroup, the association of falls with the use of donanemab cannot be established.

Phase III Study TRAILBLAZER-ALZ 2

In this study, 1736 patients, of which 1447 were in the indicated population, were randomized 1:1 to receive 700 mg of donanemab every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks via intravenous infusion (N = 860) or placebo (N = 876) for a total of up to 72 weeks. The study includes a double-blind extension period of 78 weeks duration. Dosing was continued until study completion or amyloid plaque was cleared, defined as demonstrating a plaque level of less than 25 Centiloids for two consecutive amyloid PET scans or a single PET scan demonstrating a plaque level of less than 11 Centiloids. Additionally, dose suspension was allowed for treatment-emergent ARIA. If patients were already on symptomatic treatment (acetylcholinesterase inhibitors (AChEI) and/or the N-Methyl-D-aspartate inhibitor, memantine) at study entry, these treatments could continue. Symptomatic treatments could be added or changed during the study, at the investigator's discretion. The study excluded patients who had any contraindications for MRI or PET, with pre-existing ARIA-E, greater than 4 microhaemorrhages, more than 1 area of superficial siderosis, any intracerebral haemorrhage > 1 cm or severe white matter disease.

Of the total number of patients randomized, 29 % (510/1736) were ApoE ε4 non-carriers, 54 % (930/1736) were heterozygotes, and 17 % (289/1736) were homozygotes. At baseline, mean age was 73 years, with a range of 59 to 86 years, with a mean (SD) baseline weight of 71.7 kg (15.7), with a gradual and progressive change in memory function for at least 6 months and a Mini–Mental State Examination (MMSE) score of 20 to 28 (inclusive). 57.4 % were female, 91.5 % were White, 5.7 % were of Hispanic or Latino ethnicity, 6.0 % were Asian, and 2.3 % were Black. 55.6 % of patients were on AChEI, and 20.3 % on memantine. 61.0 % of patients were on either AChEI or memantine use. The demographics of patients were similar regardless of ApoE ε4 genotype. Mean (SD) of amyloid Centiloids at baseline were 102.5 (34.5). 68.2 % and 31.8 % were in the low-medium and high tau categories, respectively. A total of 24.7 % of patients discontinued treatment in the study.

Of those, 29.3 % were patients in the donanemab arm and 20.1 % of patients in the placebo arm.

There were two primary analysis populations based on tau PET imaging at screening with flortaucipir: 1) combined population (low-medium plus high tau level population), and 2) low-medium tau level population. Early symptomatic patients with AD with no or very low tau pathology were excluded from the randomized placebo-controlled portion of the study.

The primary efficacy endpoint was change in cognition and function as measured by the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is an integrated assessment of cognition and daily function comprised of items from the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog_{13}) and the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) scale, measuring the core domains across the AD clinical continuum. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints included Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB), ADAS-Cog_{13}, ADCS-iADL.

Treatment with donanemab statistically significantly slowed clinical decline compared to placebo at week 76, with consistency across measures of cognition and function (Figure 1 and Tables 4 and 5).

Treatment effect in subgroups (age, BMI, gender, race, APOE ε4 carrier status, disease severity [MCI or mild dementia due to AD], tau terciles and concomitant symptomatic treatment) was consistent with the results in the combined study population.

Figure 1: iADRS Mean change from baseline in the indicated population and the indicated population focused on low-medium tau through 76 weeks in Study TRAILBLAZER-ALZ 2.

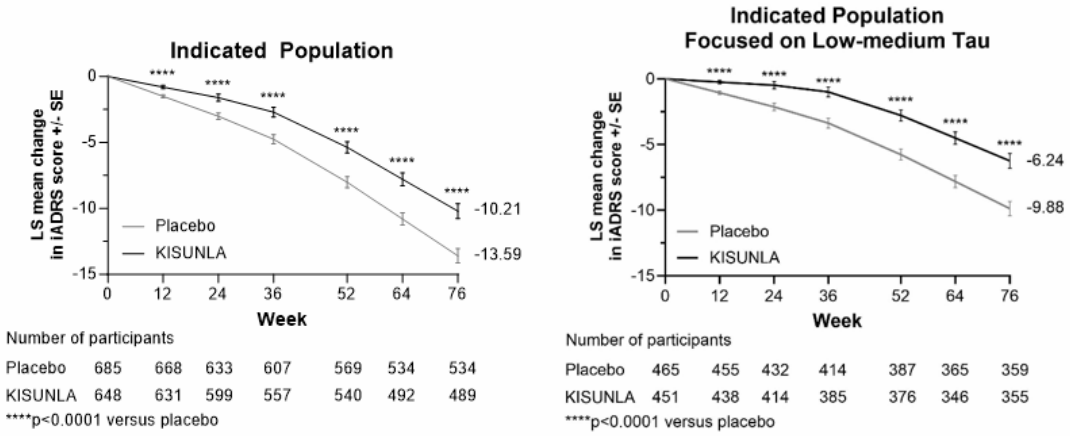


Table 4: Clinical outcomes of donanemab study TRAILBLAZER-ALZ 2 at week 76 in the indicated population and the studied combined population

	Indicated Population		**Combined Tau Population***	
Clinical endpoints	Donanemab (N = 717)	Placebo (N = 730)	Donanemab (N = 860)	Placebo (N = 876)
iADRS[a]				
Mean baseline	104.66	103.83	104.55	103.82
Change from baseline	-10.21	-13.59	-10.19	-13.11
Difference from	3.38 (1.83, 4.92)	-	2.92 (1.51, 4.33)	-

placebo (95 % CI) p-value	 p < 0.0001		 p < 0.0001	
CDR-SB[b]				
Mean baseline	3.96	3.94	3.92	3.89
Change from baseline	1.67	2.43	1.72	2.42
Difference from placebo (95 % CI) p-value	-0.77 (-1.04, -0.49) p < 0.0001	-	-0.70 (-0.95, -0.45) p < 0.0001	-
ADAS-Cog$_{13}$[a]				
Mean baseline	28.43	29.00	28.53	29.16
Change from baseline	5.37	7.06	5.46	6.79
Difference from placebo (95 % CI) p-value	-1.69 (-2.52, -0.86) p < 0.0001	-	-1.33 (-2.09, -0.57) p = 0.0006	-
ADCS-iADL[a]				
Mean baseline	48.02	47.84	47.96	47.98
Change from baseline	-4.55	-6.31	-4.42	-6.13
Difference from placebo (95 % CI) p-value	1.76 (0.81, 2.72) p = 0.0003	-	1.70 (0.84, 2.57) p = 0.0001	-

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale - Sum of Boxes; CI = confidence interval; iADRS = integrated Alzheimer's Disease Rating Scale; NCS2 = natural cubic spline with 2 degrees of freedom; MMRM = mixed model for repeated measures.

[a] Assessed using NCS2 analysis.

[b] Assessed using MMRM analysis.

* Statistically significant with adjustment for multiplicity in the graphical testing scheme

Table 5: Clinical outcomes of donanemab study TRAILBLAZER-ALZ 2 at week 76 in the indicated population focused on low-medium tau and in the low-medium tau population

	Indicated Population Focused on Low-medium Tau		Low-medium Tau Population*	
Clinical endpoints	Donanemab (N = 498)	Placebo (N = 494)	Donanemab (N = 588)	Placebo (N = 594)
iADRS[a]				
Mean baseline	105.90	105.94	105.92	105.95
Change from baseline	-6.24	-9.88	-6.02	-9.27
Difference from placebo (95 % CI)	3.64 (2.11, 5.18)		3.25 (1.88, 4.62)	
p-value	p < 0.0001		p < 0.0001	
CDR-SB[b]				
Mean baseline	3.78	3.68	3.72	3.64
Change from baseline	1.19	1.97	1.20	1.88
Difference from placebo (95 % CI)	-0.78 (-1.09, -0.47)	-	-0.67 (-0.95, -0.40)	-
p-value	p < 0.0001		p < 0.0001	
ADAS-Cog$_{13}$[a]				
Mean baseline	27.36	27.52	27.41	27.60
Change from baseline	3.22	4.98	3.17	4.69
Difference from placebo (95 % CI)	-1.76 (-2.58, -0.95)	-	-1.52 (-2.25, -0.79)	-
p-value	p < 0.0001		p < 0.0001	
ADCS-iADL[a]				
Mean baseline	48.12	48.47	48.20	48.56
Change from baseline	-2.96	-4.91	-2.76	-4.59
Difference from placebo (95 % CI)	1.96 (0.92, 2.99)	-	1.83 (0.91, 2.75)	-
p-value	p = 0.0002		p < 0.0001	

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study –

instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale - Sum of Boxes; CI = confidence interval; iADRS = integrated Alzheimer's Disease Rating Scale; NCS2 = natural cubic spline with 2 degrees of freedom; MMRM = mixed model for repeated measures.

[a] Assessed using NCS2 analysis.

[b] Assessed using MMRM analysis.

* Statistically significant with adjustment for multiplicity in the graphical testing scheme

For the primary endpoint in the combined and low-medium tau populations, additional analyses using conservative methods for the handling of missing data also favoured donanemab. The difference in mean change from placebo in the iADRS score in the combined population was 1.75 (95 % CI, 0.38 to 3.13) and in the low-medium tau population was 2.22 (95 % CI, 0.87 to 3.57).

An increase in brain volume loss relative to placebo was observed with amyloid-targeting antibodies, including donanemab. The clinical relevance of this observation is currently unclear, given the results on clinical and other biomarker endpoints in Study TRAILBLAZER-ALZ 2.

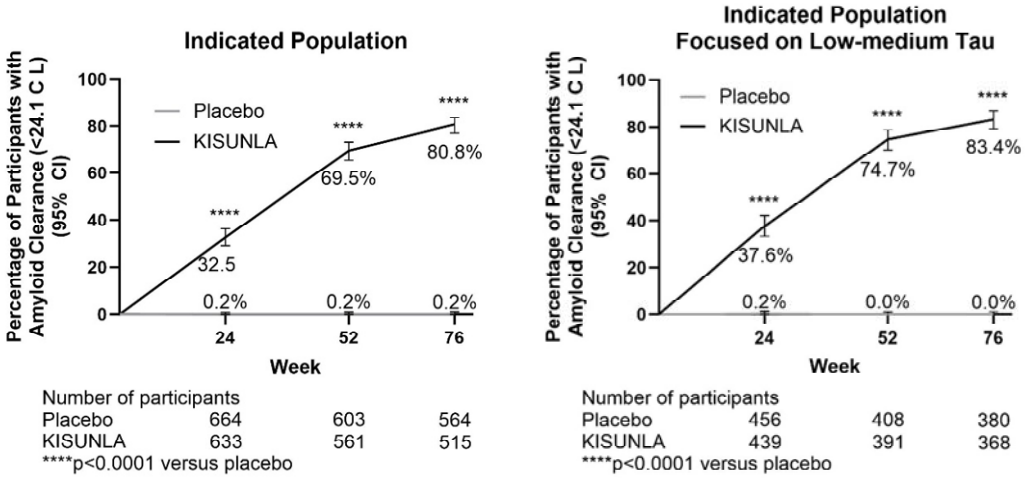
Biomarkers

The percentage of donanemab treated patients in the indicated population and indicated population focused on low-medium tau with amyloid clearance (that is, less than 24.1 Centiloids or visually negative on an amyloid PET scan) in Study TRAILBLAZER-ALZ 2 is represented in Figure 2.

Amyloid plaque reduction from baseline in donanemab treated patients, as assessed by amyloid PET, in the indicated population (LS mean change ± SE) was 65.1 ± 0.9 CL at 24 weeks, 86.3 ± 1.0 CL at 52 weeks, and 90.4 ± 1.0 CL at 76 weeks.

A reduction in plasma P-tau217 (log10) was observed with donanemab compared to placebo. In the combined population, LS mean change difference ± SE was - 0.16 ± 0.010 and - 0.22 ± 0.012 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points). Consistent with this, in the low-medium tau population, LS mean change difference ± SE was - 0.19 ± 0.011 and - 0.25 ± 0.014 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points). Consistent with this, in the indicated population, LS mean change difference ± SE was - 0.17 ± 0.011 and - 0.23 ± 0.013 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points). In the indicated population focused on low-medium tau LS mean change difference ± SE was - 0.19 ± 0.012 and - 0.26 ± 0.015 at Weeks 24 and 76, respectively, compared to placebo ($p < 0.0001$ at both time points).

Figure 2: Percentage of donanemab treated patients in the indicated population and the indicated population focused on low-medium tau achieving amyloid plaque clearance as monitored by amyloid PET over 76 weeks in study TRAILBLAZER-ALZ 2



High tau population

In the high-tau population (271 patients on donanemab and 281 patients on placebo), donanemab slowed clinical decline by 1.26 points on average (95 % CI: -1.77 to 4.28, p = 0.415) on iADRS, and - 0.69 points (95 % CI: -1.19 to -0.20, p = 0.006) on CDR-SB, at Week 76 compared with placebo. In the indicated population focused on high tau (218 patients on donanemab and 235 patients on placebo), donanemab slowed clinical decline by 1.55 points (95 % CI: -1.71 to 4.80, p = 0.351) on iADRS, and - 0.60 points (95 % CI: -1.14 to -0.05, p = 0.032) on CDR-SB, at Week 76 compared with placebo. This study was powered to demonstrate clinical efficacy in the low-medium and combined populations. The high tau population results are derived from post-hoc analyses.

Phase III, direct comparative study (TRAILBLAZER-ALZ 4)

TRAILBLAZER-ALZ 4 was a multicentre, randomised, open-label, active-comparator Phase III study investigating donanemab vs aducanumab in 148 patients with early symptomatic Alzheimer's disease. The participants were required to have evidence of amyloid beta pathology including confirmation of amyloid burden on an amyloid PET scan. Baseline flortaucipir F18 PET scan was collected but there was no tau restriction at entry. Donanemab was superior to aducanumab on the co-primary study objectives: Percentage of patients who reached amyloid plaque clearance (less than 24.1 Centiloids) on florbetapir F18 PET scan at 6 months (donanemab 37.9 % vs aducanumab 1.6 %; p < 0.001) and percentage of patients who reached amyloid plaque clearance (less than 24.1 Centiloids) on florbetapir F18 PET scan in the low-medium tau subpopulation at 6 months (donanemab 38.5 % vs aducanumab 3.8 %; p = 0.008). Comparable reduction in P-Tau217 and amyloid as measured by PET was observed regardless of baseline tau presence.

<u>Paediatric population</u>

The licensing authority has waived the obligation to submit the results of studies with donanemab in all subsets of the paediatric population in the treatment of Alzheimer's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Donanemab is for intravenous administration only.

Distribution

Following intravenous dosing, donanemab undergoes biphasic elimination. The central volume of distribution is 3.36 L with 18.7 % inter-individual variability. Peripheral volume of distribution is 4.83 L, with 93.9 % inter-individual variability.

Biotransformation

Donanemab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous IgG, hence there is no metabolic inhibition or induction of enzymatic pathways. Donanemab is not expected to be metabolized by the cytochrome P450 families of drug-metabolizing enzymes responsible for metabolism and elimination of small molecules and would, therefore, not produce any active metabolites.

Elimination

The half-life of donanemab is approximately 12.1 days. Donanemab clearance was 0.0255 L/h (24.9 % inter-individual variability).

Other intrinsic factors

The PK of donanemab was not affected by age, sex, or race, based on a population PK analysis. While body weight was found to influence both clearance and volume of distribution, the resulting changes do not suggest a need for dose adjustment.

Renal and hepatic impairment

Renal and hepatic impairment did not affect the PK of donanemab based on population PK analysis. No dose adjustment is required in patients with mild or moderate renal or hepatic impairment. However, the effect of severe hepatic and severe renal impairment on the exposure of donanemab has not been studied (see section 4.2).

5.3 Preclinical safety data

No animal studies have been performed to test donanemab for potential of carcinogenicity, genotoxicity, or fertility impairment. A weight-of-evidence assessment of all data showed a low risk of reproductive toxicity.

In cynomolgus monkeys, no adverse effects were observed with intravenous doses of donanemab up to 100 mg/kg per week for 6 weeks.

In tissue cross reactivity studies using human and monkey tissues, no binding of clinical concern was detected for donanemab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous

Polysorbate 80

Sodium citrate, dihydrate

Sucrose

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened vial

3 years

Diluted solution for infusion

Chemical and physical in-use stability has been demonstrated for up to 72 hours at 2°C to 8°C or for up to 12 hours at room temperature (20-25°C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. If dilution has taken place in controlled and validated aseptic conditions, the donanemab dosing solution may be stored for up to 72 hours at 2°C to 8°C or for up to 12 hours at room temperature 20°C to 25°C.

Storage times include the duration of infusion.

6.4 Special precautions for storage

Unopened vial

Store in a refrigerator (2 °C to 8 °C).

Keep the vial in the outer carton in order to protect from light.

Do not freeze.

Do not shake.

Once removed from the refrigerator, the vial may be stored unrefrigerated for up to 3 days at room temperature 20 °C to 25 °C, prior to preparation of the diluted solution for infusion.

Diluted solution for infusion

Do not freeze the diluted solution.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

Kisunla is supplied in a 20 ml single-dose clear type I glass vial, with a chlorobutyl elastomer stopper and an aluminium seal with a polypropylene cap.

Pack size of 1 vial.

6.6 Special precautions for disposal

Donanemab solution for infusion should be prepared and administered by a qualified healthcare professional using aseptic technique:

Allow donanemab to equilibrate to room temperature for approximately 30 minutes before preparation.

Inspect the content of the vial for particulate matter and discoloration. If particulate matter or discolorations are identified, discard the vial.

After dilution and preparation in sodium chloride 9 mg/ml (0.9 %) solution for injection (see Table 6, donanemab is administered as an intravenous infusion:

Table 6: Preparation of donanemab

Kisunla Dose (mg)	Kisunla Volume (ml)	Volume of sodium chloride 9 mg/ml (0.9 %) solution for injection (ml)	Final volume of diluted solution to be infused (ml)	Final concentration of diluted solution (mg/ml)[a]
700 mg	40 ml[b]	30 ml to 135 ml	70 ml to 175 ml	700 mg/175 ml (4 mg/ml) to 700 mg/70 ml (10 mg/ml)
1400mg	80 ml[c]	60 ml to 270 ml	140 ml to 350 ml	1400 mg/350 ml (4 mg/ml) to 1400 mg/140 ml (10 mg/ml)

[a] final concentration of 4 mg/ml to 10 mg/ml

[b] 2 vials of Kisunla

[c] 4 vials of Kisunla

Gently invert the infusion bag to mix. Do not shake.

Administer diluted solution over a period of at least 30 minutes. Administer the entire infusion solution.

Flush the line with sodium chloride 9 mg/ml (0.9 %) solution for injection at the end of the infusion.

Observe the patient post-infusion for a minimum of 30 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 14895/0338

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2024

10 DATE OF REVISION OF THE TEXT

17/03/2026