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

LEQEMBI 100 mg/mL concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 100 mg of lecanemab.
One vial of 5 mL contains 500 mg of lecanemab (500 mg/5 mL).
One vial of 2 mL contains 200 mg of lecanemab (200 mg/2 mL).

Lecanemab is a recombinant humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale yellow solution.

pH of approximately 5.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lecanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease 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 and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease.

The presence of amyloid beta (Aβ) pathology must be confirmed using approved methods 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 using a validated test (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 initial dosing regimen is 10 mg/kg administered as an intravenous (IV) infusion over approximately one hour, once every 2 weeks. After 18 months, the regimen of 10 mg/kg once every two weeks may be continued, or a transition to the maintenance dosing regimen of 10 mg/kg once every 4 weeks may be considered.

Treatment with lecanemab should be discontinued once the patient progresses to moderate Alzheimer's disease. The efficacy of continued treatment in patients with moderate Alzheimer's disease has not been established.

The duration of placebo-controlled efficacy data for lecanemab was 18 months (see section 5.1).

Dose Adjustments

No dose reductions are recommended. If a patient develops amyloid related imaging abnormalities (ARIA), see detailed Magnetic Resonance Imaging (MRI) monitoring and dosing interruption guidelines below.

Monitoring for Amyloid Related Imaging Abnormalities (ARIA)

Lecanemab 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 lecanemab.

Obtain a recent brain MRI prior to initiating treatment with lecanemab. Obtain an MRI prior to the 5th, 7th and 14th infusions. Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with lecanemab. If a patient experiences symptoms suggestive of ARIA (see section 4.4), clinical evaluation should be performed, including an MRI if indicated.

Recommendations for Dosing Interruptions or Treatment Discontinuation in Patients with ARIA

ARIA-E

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical symptoms	ARIA-E Severity on MRI[1]		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing based on clinical judgement	Suspend dosing	Suspend dosing
Symptomatic	Suspend dosing		

[1]See Table 3 for MRI radiographic severity.

Dosing may continue in asymptomatic, mild radiographic ARIA-E cases based on clinical judgement with enhanced clinical monitoring and follow-up MRI scans starting 2 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 should be performed to assess for resolution 2 to 4 months after initial identification. Once the MRI demonstrates radiographic resolution and symptoms (see section 4.4), if present, resolve, resumption of dosing should be guided by clinical judgement.

Following an initial event of ARIA-E, the rate of recurrence on resumption of treatment with lecanemab is common in ApoE ε4 non-carriers and very common in heterozygotes (see section 4.8).

ARIA-H

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical symptoms	ARIA-H Severity on MRI[1]		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing based on clinical judgement	Suspend dosing	Permanently discontinue treatment
Symptomatic	Suspend dosing		

[1]See Table 3 for MRI radiographic severity.

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

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

Following an initial event of ARIA-H, the rate of recurrence on resumption of treatment with lecanemab is very common in both ApoE ε4 non-carriers and in heterozygotes (see section 4.8).

In the event of radiographically severe ARIA-H, treatment with lecanemab should be permanently discontinued.

Radiographic Findings

The radiographic severity of ARIA associated with lecanemab was classified by the criteria shown in Table 3.

Table 3: ARIA MRI Severity Classification Criteria

ARIA Type	Radiographic Severity[1]		
	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 to 9 new incident microhaemorrhages	10 or more new incident microhaemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	>2 areas of superficial siderosis

[1]Radiographical severity is defined by the total number of new microhaemorrhages from baseline or total number of areas for superficial siderosis.

Intracerebral Haemorrhage
Lecanemab should be permanently discontinued if intracerebral haemorrhage greater than 1 cm in diameter occurs.

Delayed or missed doses

If an infusion is missed, administer the next dose as soon as possible.

Special populations

Elderly
No dose adjustment is necessary in patients ≥ 65 years (see section 5.1).

Renal impairment
No specific dose adjustment is necessary in patients with mild to moderate renal impairment (see section 5.2).

Hepatic impairment
No specific dose adjustment is needed for patients with mild to moderate hepatic impairment (see section 5.2).

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

Paediatric population
There is no relevant use of lecanemab in the paediatric population.

Method of administration

This medicinal product is for IV use only.

Lecanemab is administered as an IV infusion over approximately 1 hour once every 2 weeks during the first 18 months of treatment, and after 18 months of treatment, the regimen of 10 mg/kg once every two weeks may be continued, or a transition to the maintenance dosing regimen of 10 mg/kg once every 4 weeks may be considered. It must not be administered as an IV push or bolus injection.

Lecanemab is diluted prior to IV infusion. Infuse the entire volume of diluted solution intravenously over approximately 1 hour through an IV line containing a terminal 0.2 micron in-line filter. Flush infusion line to ensure all lecanemab is administered.

Patients should be monitored for any signs or symptoms of an infusion-related reaction (see section 4.4). The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, paracetamol, non-steroidal anti-inflammatory drugs, or corticosteroids (see sections 4.4 and 4.8).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Pre-treatment MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema, which are suggestive of cerebral amyloid angiopathy (CAA) (see section 4.4).

Treatment with lecanemab 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 lecanemab, 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.

Hypersensitivity reactions

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with lecanemab. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction and initiate appropriate therapy.

Amyloid Related Imaging Abnormalities (ARIA)

Lecanemab can cause ARIA, characterised as ARIA-E, which can be observed on MRI as brain oedema or sulcal effusions, and ARIA-H, which includes microhaemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with lecanemab generally occurs in association with an occurrence of ARIA-E.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time (see section 4.8).

Consider the benefit of lecanemab for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with lecanemab (see section 4.8).

Monitoring for ARIA and Dosing Interruption Guidelines
The recommendations for monitoring and management of ARIA-E, ARIA-H and intracerebral haemorrhage are provided in section 4.2.

ApoE ε4 Carrier Status and Risk of ARIA
Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. Patients who are homozygotes and are treated with lecanemab have a higher incidence of ARIA, including symptomatic, serious, severe radiographic, and recurrent ARIA, compared to heterozygotes and non-carriers (see section 4.8). Lecanemab is not indicated for use in patients who are homozygotes (see section 4.1).

Intracerebral haemorrhage
Intracerebral haemorrhages greater than 1 cm in diameter have occurred in patients treated with lecanemab (see section 4.8). Fatal events of intracerebral haemorrhage in patients taking lecanemab have been observed (see section 4.8).

Concomitant Antithrombotic Medication
Baseline use of antithrombotic medication (aspirin, other antiplatelet agents, or anticoagulants) was allowed in Study 301 if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Aspirin and other antiplatelet agents were used in the trial with no increase in the risk of ARIA-E, ARIA-H or intracerebral haemorrhage with lecanemab.

Because intracerebral haemorrhages have been observed in patients taking both lecanemab and anticoagulants (see section 4.8), and in patients receiving thrombolytic agents during lecanemab treatment, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g. tissue plasminogen activator) to a patient already being treated with lecanemab:

- If anticoagulation needs to be commenced during therapy with lecanemab (for example incident arterial thromboses, acute pulmonary embolism or other life-

threatening indications) then lecanemab should be paused. Lecanemab 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 to a patient being treated with lecanemab.

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

Other Risk Factors for Intracerebral Haemorrhage
Patients were excluded from enrolment in Study 301 for findings on neuroimaging (MRI) that indicated an increased risk for intracerebral haemorrhage (see section 5.1). Lecanemab should not be used in patients with pre-treatment MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema which are suggestive of CAA (see section 4.3). Caution should be exercised when considering the use of lecanemab in patients with other factors that indicate an increased risk for intracerebral haemorrhage.

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

Down syndrome

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

Infusion-related reactions

Infusion-related reactions were observed in clinical trials with lecanemab (see section 4.8); the majority were mild or moderate and occurred with the first infusion. Most reactions including severe reactions occurred during the infusion or within approximately 2.5 hours after infusion completion. Symptoms of infusion-related reactions include fever and flu-like symptoms (chills, generalised aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, fatigue, dizziness, confusion and oxygen desaturation . In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, paracetamol, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered (see section 4.2).

Patients excluded from clinical trials

Patients with a history of transient ischemic attacks (TIA), stroke or seizures within 12 months of screening, and patients with a bleeding disorder that was not under adequate control were excluded in the clinical trials with lecanemab. The safety and efficacy in these patients are unknown.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic (PK) drug interactions are expected with lecanemab.

The risk of intracerebral haemorrhage with lecanemab treatment may be increased in patients receiving anticoagulant therapy or thrombolytic agents (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no data on the use of lecanemab in pregnant women. Lecanemab should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

There are no data on the presence of lecanemab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

A decision should be made whether to discontinue breast-feeding or to discontinue lecanemab, taking into account the benefit of breast-feeding for the child and the benefit of lecanemab therapy for the woman.

Fertility

There are no data on the effects of lecanemab on human fertility.

4.7 Effects on ability to drive and use machines

Lecanemab has no or negligible influence on the ability to drive and use machines. Patients should be advised to use caution when driving or operating machinery in case they experience dizziness or confusion during treatment with lecanemab.

4.8 Undesirable effects

Summary of the safety profile

The safety of lecanemab has been evaluated in 2203 patients who received at least one dose of lecanemab.

In the double-blind, placebo-controlled period of Study 301 in patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, a total of 898 patients received lecanemab at the recommended dose of 10 mg/kg every 2 weeks, of which 757 patients were non-carriers or heterozygotes (the indicated population).

Of the patients treated with lecanemab 31% (278/898) were non-carriers, 53% (479/898) were heterozygotes and 16% (141/898) were homozygotes. With the exception of events of ARIA, the safety profile was the same across genotypes.

In the indicated population, the most common adverse reactions were infusion-related reaction (26%), ARIA-H (13%), fall (11%), headache (11%) and ARIA-E (9%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials are listed below in Table 4. The adverse reactions are listed by MedDRA System Organ Class and categories of frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each System Organ Class and frequency grouping, adverse reactions are presented in order of decreasing seriousness

Table 4: Adverse reactions

System Organ Class (SOC)	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Immune system disorders		Hypersensitivity reactions	Anaphylaxis
Nervous system disorders	ARIA-H[1] Headache	ARIA-E[2]	Intracerebral haemorrhage
Cardiac disorders		Atrial fibrillation	
Skin and subcutaneous tissue disorders		Rash[3]	
General disorders and administration site conditions	Infusion-related reactions		

[1]ARIA-H: Amyloid related imaging abnormality-microhaemorrhage and haemosiderin deposit; Superficial siderosis of central nervous system, and Cerebellar microhaemorrhage.

[2]ARIA-E is common in the indicated population and very common in the homozygote population.

[3]Rash: acne, erythema, infusion-site rash, injection-site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

Description of selected adverse reactions

Incidence of ARIA in the Indicated Population

Symptomatic ARIA occurred in 2% (16/757) of patients on lecanemab who are non-carriers and heterozygotes in Study 301. Serious symptoms associated with ARIA that required hospitilisation were reported in 0.4% (3/757) of patients on lecanemab. Clinical symptoms associated with ARIA resolved in 75% (12/16) of patients during the 18-month study period; clinical symptoms in 50% of these patients resolved within 3 days.

Including asymptomatic radiographic events, ARIA was observed in 17% (128/757) of patients on lecanemab compared to 7% (55/764) of patients on placebo.

ARIA-E was observed in 9% (67/757) of patients on lecanemab compared with 1% (10/764) of patients on placebo. The majority of ARIA-E was asymptomatic, with symptomatic ARIA-E reported in 2% (12/757) patients on lecanemab and no patients on placebo

ARIA-H was observed in 13% (98/757) of patients on lecanemab compared with 7% (52/764) of patients on placebo. The majority of ARIA-H was asymptomatic, with symptomatic ARIA-H reported in 0.8% (6/757) of patients on lecanemab and 0.1% (1/764) on placebo. ARIA-H and ARIA-E can occur together. There was no increase

in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for lecanemab compared to placebo.

The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA-E can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients on lecanemab was mild in 4% (31/757), moderate in 4% (33/757), and severe in 0.3% (2/757) of patients. Resolution on MRI occurred in 64% (43/67) of patients by 12 weeks, 87% (58/67) by 17 weeks, and 100% (67/67) overall after detection, compared with 80% (8/10) of patients on placebo.

The maximum radiographic severity of ARIA-H microhaemorrhage in patients on lecanemab was mild in 8% (60/757), moderate in 1% (8/757), and severe in 1% (10/757) of patients; ARIA-H superficial siderosis was mild in 3% (26/757), moderate in 0.5% (4/757), and severe in 0.3% (2/757) of patients. ARIA-H stabilised in 79% (77/97) of patients on lecanemab compared with 75% (39/52) of patients on placebo, either at the first follow-up MRI or within 20 weeks for most patients.

See Table 3 in section 4.2 for MRI radiographic severity.

Recurrence of ARIA in the Indicated Population
ARIA-E was observed in 9% (67/757) of patients on lecanemab, of which 88% (59/67) continued on lecanemab with or without dose interruption. Among those that continued lecanemab, 14% (8/59) experienced a recurrence of ARIA-E.

ARIA-H (with or without concurrent ARIA-E) was observed in 13% (98/757) of patients on lecanemab and 7% (52/764) of patients on placebo, of which 80% (78/98) and 77% (40/52) continued treatment with or without dose interruption, respectively. Among those that continued, 36% (28/78) of patients on lecanemab and 30% (12/40) of patients on placebo experienced a recurrence of ARIA-H.

Intracerebral Haemorrhage in the Indicated Population
Intracerebral haemorrhage was reported in 0.5% (4/757) of patients on lecanemab compared to 0.1% (1/764) of patients on placebo.

The incidence of intracerebral haemorrhage was 0.3% (1/286) of patients on lecanemab with a concomitant antithrombotic medication at the time of the event compared to 0.7% (3/450) of patients who did not. Patients taking lecanemab with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral haemorrhage of 1.5% (1/68 patients) compared to no patients on placebo.

Fatal events of intracerebral haemorrhage have been observed in patients taking lecanemab.

APOE ε4 Carrier Status and Risk of ARIA
In study 301, the incidence of ARIA was lower in non-carriers (13% lecanemab vs 4% placebo) and heterozygotes (19% lecanemab vs 9% placebo) than in homozygotes (45% lecanemab vs 22% placebo). Among patients treated with lecanemab, symptomatic ARIA-E occurred in 1% of non-carriers and 2% of heterozygotes compared with 9% of homozygotes. Serious events of ARIA occurred in approximately 1% of non-carriers and heterozygotes and 3% of homozygotes. Among patients treated with lecanemab, the rate of severe radiographic ARIA-E was lower in non-carriers 0% (0/278) and heterozygotes 0.4% (2/479) compared to homozygotes

5% (7/141). The rate of severe radiographic ARIA-H was lower in non-carriers 1% (3/278) and heterozygotes 2% (10/479) compared to homozygotes 14% (19/141).

Among the patients who experienced an event of ARIA-E and continued on lecanemab with or without dose interruption, the rates of recurrence were 9% (1/11) in non-carriers, 15% (7/48) in heterozygotes and 54% (20/37) in homozygotes.

Among the patients who experienced an event of ARIA-H and continued on lecanemab with or without dose interruption, the rates of recurrence were 22% (5/23) in non-carriers (compared with 14% [1/7] on placebo), 42% (23/55) in heterozygotes (compared with 33% [11/33] on placebo), and 62% (29/47) in homozygotes (compared with 50% [12/24] on placebo).

Infusion-related Reactions
Infusion-related reactions were observed in 26% (237/898) of patients treated with lecanemab compared to 7% of patients on placebo; and 75% (178/237) occurred with the first infusion. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity, severe infusion-related reactions were reported in less than 1% of patients. Infusion-related reactions resulted in discontinuations in 1% (12/898) of patients on lecanemab. The incidence of infusion-related reactions was similar regardless of ApoE ε4 genotype.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play and Apple App store.

4.9 Overdose

There is limited clinical experience with lecanemab overdose.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment initiated immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, psychoanaleptics, anti-dementia drugs, other anti-dementia drugs, ATC code: N06DX04

Mechanism of action

Lecanemab is a humanised IgG1 mAb which demonstrates low affinity for Aβ monomers, while it binds with high selectivity to Aβ aggregate species, with preferential activity for toxic

soluble Aβ protofibrils. Lecanemab binds these aggregate Aβ species to neutralize and clear them from the brain.

Pharmacodynamic effects

The effect of lecanemab on amyloid beta plaque levels in the brain was evaluated using PET imaging (18F-florbetapir tracer). The PET signal was quantified using both the Standard Uptake Value Ratio (SUVR) and Centiloid scale to estimate levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology. Lecanemab reduced amyloid beta plaque in a dose- and time-dependent manner in the dose-ranging study 201 and in a time-dependent manner in single-dosing regimen Study 301 through Week 79 compared with placebo. Improvements relative to placebo were seen on biomarkers of amyloid (plasma Aβ42/40, CSF Aβ[1-42]) and downstream biomarkers of tau (tau PET, plasma p-tau181), neurodegeneration (CSF t-tau, CSF neurogranin) and gliosis (GFAP).

During an off-treatment period in Study 201 (range from 9 to 59 months; mean of 24 months), amyloid began to increase with a mean rate of increase of 2.6 Centiloids/year, however, treatment difference relative to placebo after the 18-month double-blind period in Study 201 was maintained.

In Study 301, after Week 79 of treatment with lecanemab 10 mg/kg every two weeks, 67% of patients had amyloid levels less than 30 Centiloids as measured by PET. Patients who did not have reduction of amyloid plaques to these levels at Week 79 tended to have higher amyloid PET levels at baseline. The percentage of patients achieving amyloid levels less than 30 Centiloids after continuous treatment with lecanemab 10 mg/kg every two weeks is predicted to increase over time. After Week 79, it is predicted that reducing the frequency of 10 mg/kg to once every 4 weeks will also continue the reduction in amyloid beta plaque levels.

A reduction in plasma p-tau181 (Table 6), CSF p-tau181, and CSF t-tau was observed with lecanemab 10 mg/kg every two weeks compared to placebo. Exposure-response modelling predicts that a dose of 10 mg/kg every 4 weeks after 18 months of treatment with 10 mg/kg every two weeks will maintain the reduction in plasma p-tau181.

Clinical efficacy and safety

The efficacy and safety of lecanemab were evaluated in the pivotal Phase III Study 301 and the dose finding Study 201. The core phases of both studies were double-blind, placebo-controlled, parallel-group, randomised studies in patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia (patients with confirmed presence of brain amyloid pathology as measured by amyloid PET or CSF t-tau/Aβ[1-42] testing and that met the National Institute of Aging-Alzheimer's Association [NIA-AA] clinical criteria for mild cognitive impairment due to Alzheimer's disease [62% of patients in Study 301; 65% of patients in Study 201] or mild dementia stage of disease [38% of patients in Study 301; 36% of patients in Study 201]).

In both studies, patients were enroled with a CDR global score of 0.5, or 1.0 and Memory Box score of 0.5 or greater. All patients had a Mini-Mental State Examination (MMSE) score of ≥22 and ≤30, and had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale) (WMS-IV LMII). Patients were enroled with or without concomitant approved symptomatic therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. Exclusion criteria included evidence of history of TIA, stroke or seizures within 12 months of screening or significant pathological findings on brain MRI including those indicating an increased risk for intracerebral

haemorrhage. These included findings suggestive of CAA (prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis, vasogenic oedema) or other lesions (aneurysms, vascular malformation) that could potentially increase the risk of intracerebral haemorrhage. Patients with bleeding disorders not under adequate control were also excluded. The dose of 10 mg/kg once every 2 weeks was assessed in the 18-month placebo-controlled portions of Study 201 and Study 301 and continued in the optional long-term extension in each study. Transitioning to 10 mg/kg once every 4 weeks after 18 months of dosing is supported by pharmacokinetic and pharmacodynamic modelling using observed data (see section 4.2).

In Study 301, 1795 patients were randomised to receive lecanemab 10 mg/kg every 2 weeks or placebo for 18 months, of which 1521 were in the indicated population. Of the total number of patients randomised 31% were non-carriers, 53% were heterozygotes and 16% were homozygotes. At baseline, the median age of randomised patients was 72 years, with a range of 50 to 90 years. Fifty-two percent of patients were women; 77% were Caucasian, 17% were Asian, 3% were Black. 57% of patients were receiving concomitant approved symptomatic therapies for Alzheimer's disease. Comorbidities included hyperlipidaemia (60%), hypertension (55%), obesity (17%), ischemic heart disease (16%) and diabetes (15%). The demographics of patients were similar regardless of ApoE ε4 genotype.

The randomisation was stratified according to clinical subgroup; the presence or absence of concomitant symptomatic medication for Alzheimer's disease at baseline; ApoE ε4 carrier status; region and by disease stage (mild cognitive impairment or mild Alzheimer's disease).

In Study 201, 856 patients were randomised to receive one of 5 doses (161 of which were randomised to the recommended dosing regimen of 10 mg/kg every two weeks) of lecanemab or placebo (n=247) for 18 months. Of the total number of patients randomised, 71% were ApoE ε4 carriers and 29% were ApoE ε4 non-carriers. During the study the protocol was amended to no longer randomise ApoE ε4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ε4 carriers who had been receiving lecanemab 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. As a result, in the lecanemab 10 mg/kg once every two weeks arm, 30% of patients were ApoE ε4 carriers and 70% were ApoE ε4 non-carriers. At baseline, the mean age of randomised patients was 71 years, with a range of 50 to 90 years. Fifty percent of patients were male and 90% were White. 46% of patients were receiving concomitant approved symptomatic therapies for Alzheimer's disease.

Patients included in Study 201 and Study 301 had typical forms of memory-predominant Alzheimer's disease. The safety and efficacy of treatment in patients with atypical Alzheimer's disease syndromes (without memory-predominant Alzheimer's disease) is not established.

Study 301 results

The primary efficacy outcome was change from baseline at 18 months in the Clinical Dementia Rating – Sum of Boxes (CDR-SB).

Key secondary efficacy endpoints included change from baseline after 18 months for the following measures: Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks (ADAS-Cog14), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL).

In the overall population, lecanemab treatment met the primary endpoint and slowed disease progression on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months (-0.45 [-27%], p=0.00005).

In the indicated population (ApoE ε4 heterozygotes and non-carriers), lecanemab treatment slowed disease progression on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months (-0.58 [-33%], p<0.00001).

Statistically significant differences (p<0.01) between treatment groups were also seen in the results for ADAS-Cog14 and ADCS-MCI-ADL at 18 months; see Table 5 and Figures 1, 2, and 3.

Table 5: Results for CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL in Study 301

	Indicated Population		**Overall Population***	
Clinical Endpoints	**Lecanemab 10 mg/kg every 2 weeks**	**Placebo**	**Lecanemab 10 mg/kg every 2 weeks**	**Placebo**
CDR-SB[1]	N=723	N=743	N=859	N=875
Mean baseline	3.17	3.22	3.17	3.22
Adjusted mean change from baseline at 18 months	1.151	1.730	1.213	1.663
Difference from placebo (95% CI)	-0.579 (-0.811, -0.347) (p<0.00001)		-0.451 (-0.669, -0.233) (p=0.00005)	
ADAS-Cog14	N=719	N=740	N=854	N=872
Mean baseline	24.48	24.40	24.45	24.37
Adjusted mean change from baseline at 18 months	4.211	5.845	4.140	5.581
Difference from placebo (95% CI)	-1.633 (-2.555, -0.712) (p=0.00052)		-1.442 (-2.270, -0.613) (p=0.00065)	
ADCS-MCI-ADL	N=656	N=675	N=783	N=796
Mean baseline	41.3	40.9	41.2	40.9
Adjusted mean change from baseline at 18 months	-3.469	-5.703	-3.484	-5.500
Difference from placebo (95% CI)	2.234 (1.342, 3.126) (p<0.00001)		2.016 (1.208, 2.823) (p<0.00001)	

[1]The CDR-SB is a global scale of cognition and function. The CDR-SB evaluates 6 domains (Memory, Orientation, Judgement & Problem Solving, Community Affairs, Home & Hobbies, Personal Care), with each of the domains scored on the following scale of impairment: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), or 3 (severe). The CDR-SB ranges from cognitively normal [0] through to severe dementia [18]. The relevant portion of the CDR-SB scale for early Alzheimer's disease ranges from 0.5 to 6.
* Primary analysis

In the overall population, for the primary endpoint, an additional analysis using conservative methods for the handling of missing data gave similar results, with an adjusted mean change in CDR-SB of -0.401 (95% CI, -0.622 to -0.180).

In the indicated population, for the primary endpoint, an additional analysis using conservative methods for the handling of missing data gave similar results, with an adjusted mean change in CDR-SB of -0.518 (95% CI, -0.755 to -0.280).

Figure 1: Adjusted Mean Change from Baseline in CDR-SB in Study 301 for the Indicated Population

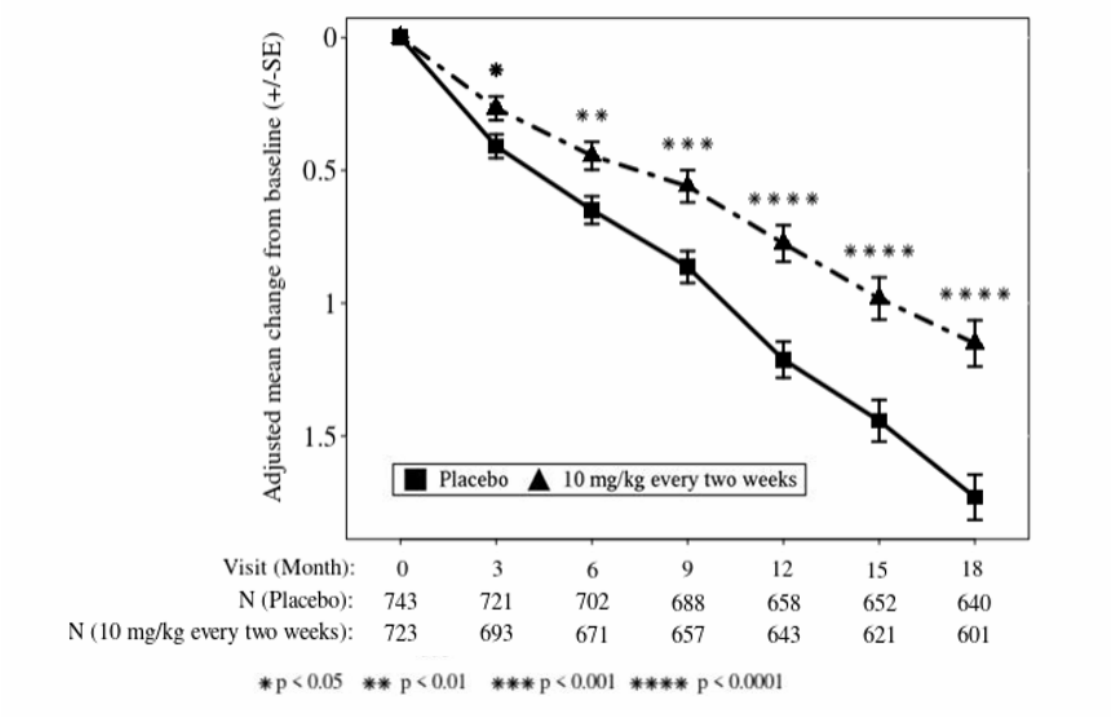


Figure 2: Adjusted Mean Change from Baseline in ADAS-Cog14 in Study 301 for the Indicated Population

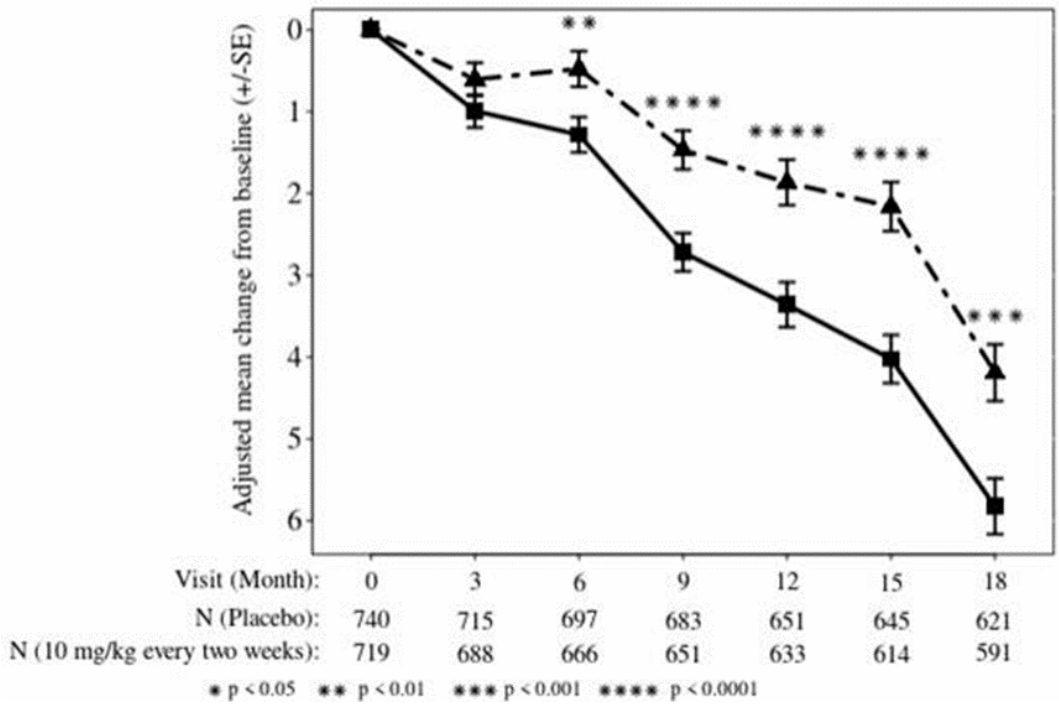
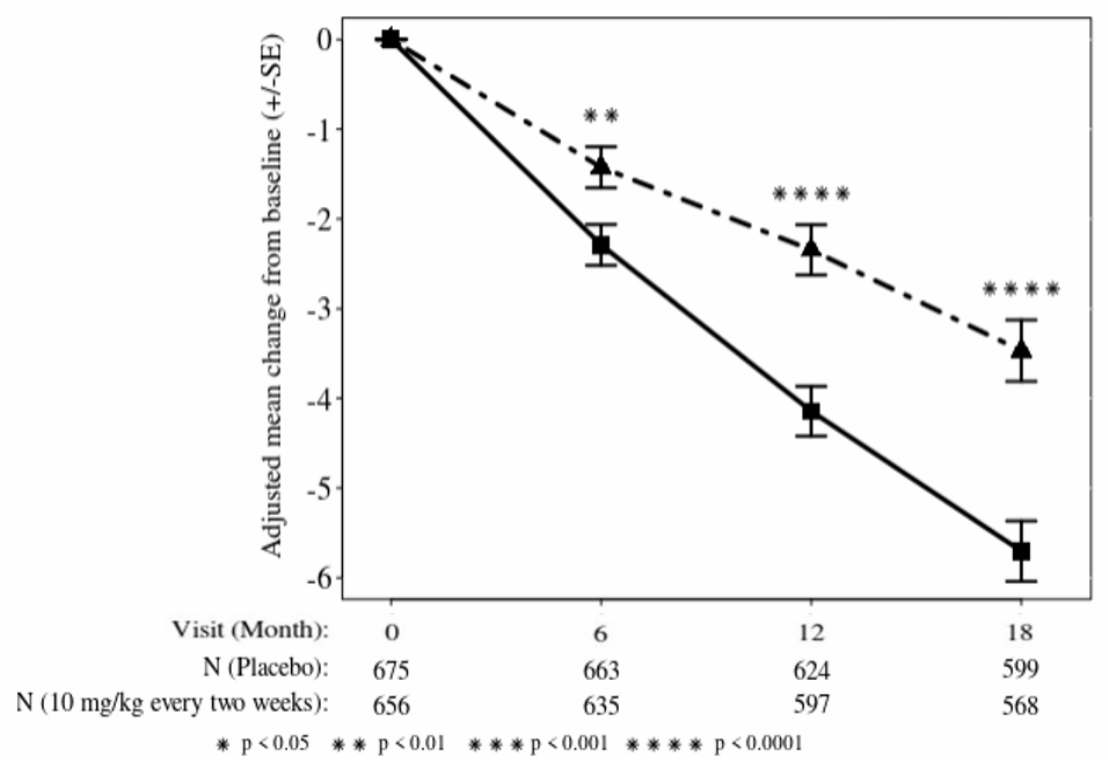


Figure 3: Adjusted Mean Change from Baseline in ADCS-MCI-ADL in Study 301 for the Indicated Population



An increase in brain volume loss relative to placebo was observed with anti-βamyloid antibodies, including lecanemab. The clinical relevance of this observation is currently unclear, given the results on clinical and other biomarker endpoints in Study 301.

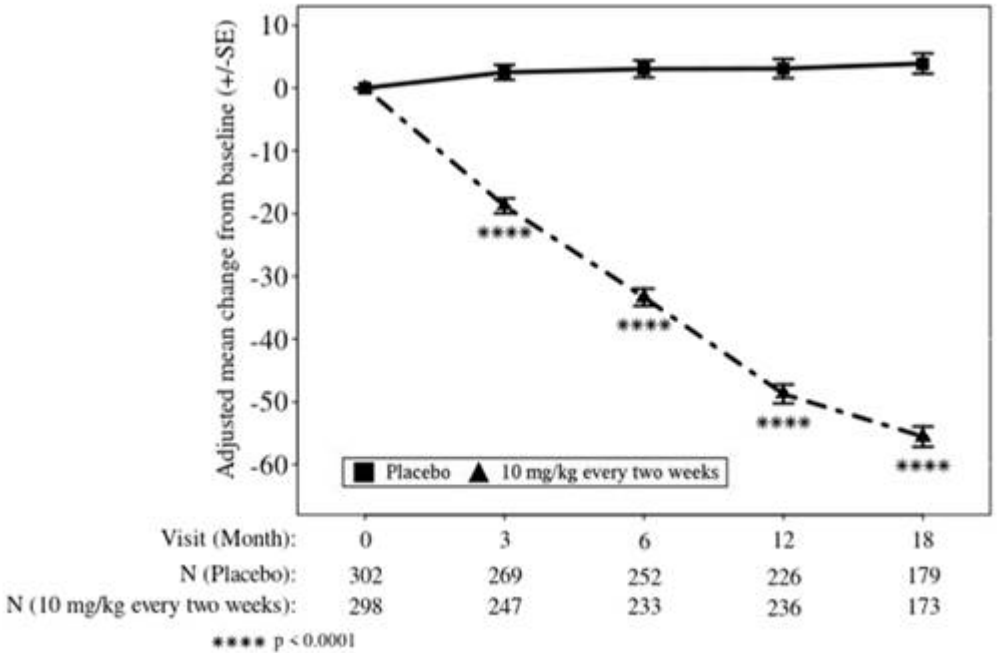
APOE ε4 status

Both ApoE ε4 carriers and ApoE ε4 non-carriers showed statistically significant treatment differences for the primary endpoint and all secondary endpoints. In an exploratory subgroup analysis of homozygotes, which represented 15% of the trial population, a treatment effect was not observed with lecanemab treatment on the primary endpoint, CDR-SB, compared to placebo, although treatment effects that favoured lecanemab were observed for the secondary clinical endpoints, ADAS-Cog 14 and ADCS-MCI-ADL. Treatment effects on disease-relevant biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau 181) also favoured lecanemab in the ApoE ε4 homozygous subgroup.

Biomarkers

In Study 301, change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels was a key secondary endpoint. The mean change from baseline relative to placebo was statistically significant for lecanemab 10 mg/kg every 2 weeks at 18 months ($p<0.00001$) in the overall population and the indicated population. The magnitude of the reduction was time-dependant (see Figure 4). Reductions in amyloid beta plaque compared to placebo were seen starting at Week 13.

Figure 4: Reduction in Brain Amyloid Beta Plaque (Adjusted Mean Change from Baseline in Amyloid Beta PET Centiloids) in Study 301 for the Indicated Population



An increase in plasma Aβ42/40 ratio and decrease in plasma p-tau181 was observed with lecanemab 10 mg/kg every two weeks dosing compared to placebo, see Table 6.

Table 6: Biomarkers Results for Lecanemab in Study 301

	Indicated Population		**Overall Population**	
Biomarker Endpoints	**Lecanemab 10 mg/kg every 2 weeks**	**Placebo**	**Lecanemab 10 mg/kg every 2 weeks**	**Placebo**
Plasma Aβ42/40 ratio	N=674	N=685	N=797	N=805
Mean Baseline	0.088	0.088	0.088	0.088
Adjusted mean change from Baseline at Week 53	0.006	-0.001	0.006	-0.000
Difference from placebo	0.007 (p<0.00001)[1]		0.007 (p<0.00001)[1]	
Adjusted mean change from Baseline at Week 77	0.008	0.000	0.008	0.001
Difference from placebo	0.008 (p<0.00001)[1]		0.007 (p<0.00001)[1]	
Plasma p-tau181 (pg/mL)	N=628	N=635	N=746	N=752
Mean Baseline	3.669	3.768	3.696	3.740
Adjusted mean change from Baseline at Week 53	-0.491	0.306	-0.466	0.278
Difference from placebo	-0.796 (p<0.00001)[1]		-0.744 (p<0.00001)[1]	
Adjusted mean change from Baseline at Week 77	-0.596	0.230	-0.575	0.201
Difference from placebo	-0.825 (p<0.00001)[1]		-0.776 (p<0.00001)[1]	

[1] P-values were not statistically controlled for multiple comparisons

A sub study was conducted in Study 301 to evaluate the effect of lecanemab on neurofibrillary tangles composed of tau protein using PET imaging (^{18}F-MK6240 tracer). The PET signal was quantified using the SUVR method to estimate brain levels of tau in brain

regions expected to be affected by Alzheimer's disease pathology (whole cortical grey matter, meta-temporal, frontal, cingulate, parietal, occipital, medial temporal, and temporal) in the study population compared to a brain region expected to be spared of such pathology (cerebellum). The adjusted mean change from baseline in tau PET SUVR, relative to placebo, was in favour of lecanemab in the medial temporal ($p<0.05$), meta temporal ($p<0.05$), and temporal ($p<0.05$) regions. No statistically significant differences were observed for the whole cortical grey matter, frontal, cingulate, parietal, or occipital regions.

Study 201 results
The primary endpoint was change from baseline on the ADCOMS, a weighted composite score consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog14 at Week 53. Lecanemab had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at Week 53, which did not meet the prespecified success criterion of 80%.

Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79. Results for clinical assessments showed slowing of disease progression on change from baseline CDR-SB and ADAS-Cog 14 scores at Week 79 in the lecanemab group than in patients on placebo (CDR-SB: -0.41 [26%], 90% CI [-0.82, 0.03]; ADAS-Cog 14: -2.31 [47%], 90% CI [-3.91, -0.72]).

Immunogenicity
The immunogenicity of lecanemab has not been sufficiently evaluated due to limitation of anti-drug antibody assay. The impact of ADA on pharmacokinetics, efficacy and safety has not been sufficiently evaluated.

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

5.2 Pharmacokinetic properties

The PK of lecanemab was characterised in Phase 1 studies using a population PK analysis with concentration data collected from 1619 patients with Alzheimer's disease who received lecanemab in single or multiple doses. Steady state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg every 2 weeks treatment and systemic accumulation was 1.5-fold.

Lecanemab is a mAb that targets soluble and insoluble aggregated forms of amyloid beta, and is not expected to be involved in cytokine modulated pathways.

Distribution

The mean value (95% CI) for central volume of distribution at steady state is 3.24 (3.18-3.30) L. The mean (SD) CSF concentration ratio is 0.29% (0.140).

Elimination

Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous IgGs. Lecanemab clearance (95% CI) is 0.370 (0.353-0.384) L/day. The terminal half-life is 5 to 7 days.

Linearity/non-linearity

Lecanemab exhibits linear pharmacokinetics in the range 0.3 mg/kg to 15 mg/kg.

Hepatic or renal impairment

Lecanemab elimination occurs through normal degradative pathways for immunoglobulins, and the systemic clearance should not be affected by renal or hepatic impairment. Liver function biomarkers (ALT, AST, ALP, total bilirubin) and creatinine clearance did not affect the PK parameters of lecanemab.

Other factors

Sex, body weight, race and albumin were found to impact exposure to lecanemab. However, none of these covariates were found to be clinically significant.

Drug Interactions

Elimination of lecanemab is likely to occur through normal degradation pathways for immunoglobulins and the clearance should not be affected by small molecule concomitant medications. Therefore, it is not expected that lecanemab will cause or be susceptible to drug interactions with concomitantly administered agents.

Concurrent use of symptomatic treatments for Alzheimer's disease did not impact the effectiveness of lecanemab or the type or rate of adverse events.

5.3 Preclinical safety data

Carcinogenesis

Carcinogenicity studies have not been conducted. No lecanemab-related proliferative lesions were observed in toxicology studies up to 39 weeks in cynomolgus monkeys or up to 18 weeks in aged Tg2576 mice.

Mutagenesis

Genotoxicity studies have not been conducted.

Impairment of Fertility

Fertility studies have not been conducted for lecanemab. No effects on reproductive organs in cynomolgus monkeys in repeated-dose studies up to 39 weeks were noted at doses 27 times the clinical exposures (based on AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Arginine hydrochloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened vial: 42 months.

After dilution, an immediate use is recommended.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

However, from a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Store in the original package in order to protect from light.
Do not freeze or shake vials.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml concentrate in a vial (Type I glass) with a stopper (elastomere) – pack size of 1.
5 ml concentrate in a vial (Type I glass) with a stopper (elastomere) – pack size of 1.

6.6 Special precautions for disposal

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Discard the vial if visible particles are observed.

Check that the lecanemab solution is opalescent and colourless to pale yellow.

Preparation of infusion solution
Calculate the dose, the total volume of lecanemab solution required, and the number of vials needed based on the patient's actual body weight. Each vial contains a lecanemab concentration of 100 mg/mL.

Withdraw the required volume of lecanemab from the vial(s) and add to 250 mL 0.9% sodium chloride solution for injection.

Gently invert the infusion bag containing the lecanemab diluted solution to mix completely. Do not shake.

Administration of infusion solution
Prior to infusion, allow the lecanemab diluted solution to warm to room temperature.

Infuse the entire volume of lecanemab intravenously over approximately 1 hour through an IV line containing a terminal low-protein binding 0.2 micron in-line filter. Flush infusion line to ensure all lecanemab is administered.

Observe patients during the infusion. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction (see section 4.4).

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

7 MARKETING AUTHORISATION HOLDER

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