Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Leqembi 100 mg/ml concentrate for solution for infusion

Lecanemab

PLGB 33967/0027

Eisai Europe Limited

LAY SUMMARY

Leqembi 100 mg/ml concentrate for solution for infusion
Lecanemab

This is a summary of the Public Assessment Report (PAR) for Leqembi 100 mg/ml concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Leqembi in this lay summary for ease of reading.

For practical information about using Leqembi, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Leqembi and what is it used for?

This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Leqembi is used to treat the early stages of Alzheimer's disease in adults who carry one copy of a gene called apolipoprotein E4, also known as ApoE4, or in adults who do not carry this gene.

The patient's healthcare provider will perform testing to make sure that Leqembi is right for the patient.

Alzheimer's disease is an illness that affects the brain. Communications between brain cells become blocked due to amyloid beta plaques. This eventually leads to problems with memory, thinking and behaviour. Alzheimer's disease symptoms can be different for everyone. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks.

How does Leqembi work?

Leqembi contains the active substance lecanemab. Lecanemab is a monoclonal antibody. Antibodies are found naturally in our blood and help us to fight infection. Monoclonal antibody therapies mimic natural antibodies but are made in a laboratory. They work by binding to a target protein to reduce the harmful effect of that protein. Lecanemab binds to a protein called amyloid beta, which is involved in Alzheimer's disease.

In Alzheimer's disease, clumps of amyloid beta protein form plaques in the brain. Leqembi works by binding to these clumps and reducing them. This slows down progression of early Alzheimer's disease.

How is Leqembi used?

The pharmaceutical form of this medicine is a concentrate for solution for infusion and the route of administration is intravenous infusion (drip into a vein).

Leqembi is given to the patient under the supervision of a healthcare professional.

Each infusion will last approximately 1 hour.

Dosage:
The recommended dose is 10 milligrams per kilogram of body weight (mg/kg). It should be given to the patient every 2 weeks.

MRI scans:
The patient's doctor will arrange brain scans (magnetic resonance imaging [MRI]) before treatment and before the fifth, seventh and fourteenth doses of Leqembi. This is routine monitoring to check if the patient has amyloid-related imaging abnormalities (ARIA). Additional scans can be performed at other times during treatment if the patient's doctor thinks they are needed. The patient's doctor may stop treatment temporarily, depending on the MRI results.

Missing an infusion:
If the patient misses an infusion of Leqembi, they should talk to their doctor to arrange to have it as soon as possible. They should not wait until their next planned infusion.

Stopping Leqembi:
The patient's doctor may recommend pausing or stopping treatment, depending on the patient's clinical test results.

For further information on how Leqembi is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask their doctor or nurse for further information if they have any questions concerning the medicine.

What benefits of Leqembi have been shown in studies?
Leqembi was evaluated in a main study (study 301) involving 1,795 patients with early Alzheimer's disease, including patients with mild cognitive impairment or mild dementia and confirmed presence of amyloid beta pathology. 1,521 patients were in the indicated population. Patients were given either Leqembi (at a dose of 10 mg/kg, once every two weeks) or placebo (a dummy infusion).

The study looked at the change from baseline at 18 months in the Clinical Dementia Rating scale Sum of Boxes (CDR-SB) score, which is a measure of the patient's cognition and function that is obtained by interviewing patients and their care partners. Leqembi demonstrated a statistically significant reduction in clinical decline on the CDR-SB scale when compared with placebo for both the overall and indicated population.

In another study (study 201), 856 patients with early Alzheimer's disease (including patients with mild cognitive impairment or mild dementia and confirmed presence of amyloid beta pathology) were given one of 5 doses of Leqembi or placebo for 18 months. The study included 161 patients who were given the recommended dosing regimen of 10 mg/kg, once every two weeks. The study looked at the change from baseline in the Alzheimer's Disease Composite Score (ADCOMS).

The study showed that after 12 months of treatment, Leqembi had a 64% likelihood of 25% or greater slowing of disease progression compared to placebo, however this did not meet the success criterion of the study of 80%. After 18 months of treatment, Leqembi showed slowing of disease progression on CDR-SB and ADAS-Cog 14 (another clinical measure of disease) scores compared to placebo.

In both studies, at 18 months there was a statistically significant reduction in amyloid beta plaque levels in the brain for Leqembi, compared to placebo.

What are the possible side effects of Leqembi?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Leqembi (which may affect more than 1 in 10 people) are:

- Small spots of bleeding in or on the surface of the brain (ARIA-H)
- Infusion-related reactions. Signs include fever, flu-like symptoms such as chills, body aches, feeling shaky and joint pain, feeling sick (nausea), being sick (vomiting), dizziness or light-headedness, changes in heart rate or feeling like the chest is pounding, difficulty breathing or shortness of breath.
- Headache.

Why was Leqembi approved?
It was concluded that Leqembi has been shown to be effective in treating the early stages of Alzheimer's disease in adults who carry one copy of a gene called apolipoprotein E4, also known as ApoE4, or in adults who do not carry this gene. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Leqembi has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Leqembi?"

What measures are being taken to ensure the safe and effective use of Leqembi?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Leqembi. The RMP details the important risks of Leqembi, how these risks can be minimised, any uncertainties about Leqembi (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Leqembi:

List of Important Risks and Missing Information	
Important identified risks	• Amyloid-related imaging abnormalities - oedema/effusion (ARIA-E) • Amyloid-related imaging abnormalities - haemosiderin deposition (ARIA-H [cerebral microhaemorrhage and superficial siderosis]) • Amyloid-related imaging abnormalities (ARIA) intracerebral haemorrhage greater than 1 cm in diameter
Important potential risks	None
Missing information	• Accelerated brain volume loss • Long-term safety

Additional risk minimisation measures are required, including a controlled access programme to promote the safe and effective use of lecanemab that registers all patients before they start treatment and educational materials in the form of a patient alert card and a healthcare professional guide.

A post-authorisation safety study will be conducted to investigate the safety and benefit-risk profile of lecanemab in routine clinical practice, particularly in relation to the incidence and severity of ARIAs and intracerebral haemorrhage, and long-term safety.

Long-term safety will also be investigated in the open-label extension of Study 301.

Accelerated brain volume loss will be evaluated in Study 303, which includes subjects with preclinical Alzheimer's disease

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Leqembi are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and is satisfactory.

Other information about Leqembi

A marketing authorisation application for Leqembi was received on 19 May 2023 and a marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 22 August 2024.

The full PAR for Leqembi follows this summary.

This summary was last updated in October 2024.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Leqembi 100 mg/ml concentrate for solution for infusion (PLGB 33967/0027) could be approved.

The product is approved for the following indication:
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 SmPC section 5.1).

The active substance, 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 neutralise and clear them from the brain.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), as a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This medicine was developed utilising the Innovative Licensing and Access Pathway (ILAP). The ILAP aims to accelerate the time to market for innovative medicines, thereby facilitating patient access to them. As part of the pathway, the medicine was granted an Innovation Passport on 17 February 2023, which provided access to enhanced regulatory and other stakeholder input and support for the safe, timely and efficient development of the product.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the granting of a class waiver CW/1/2011 and CW/1/2015.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) in February 2024. At that time, on grounds relating to safety and efficacy, the Commission was unable to advise the grant of the Marketing Authorisation for the product. Further data was presented to the CHM on 31 May 2024, 27 June 2024 and 25 July 2024. On the further evidence before it, the CHM advised the grant of a Marketing Authorisation.

A marketing authorisation application for Leqembi was received on 15 May 2023, and a marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 22 August 2024.

II QUALITY ASPECTS

II.1 Introduction

This product contains 100 mg of lecanemab in each ml of concentrate for solution for infusion. One vial of 5 ml of concentrate for solution for infusion contains 500 mg of lecanemab (500 mg/5 ml). One vial of 2 ml of concentrate for solution for infusion 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.

In addition to lecanemab, this product also contains the excipients histidine, histidine hydrochloride monohydrate, arginine hydrochloride, polysorbate 80 and water for injections.

The finished product is packaged in vials (Type I glass) with a stopper (elastomere) in a pack size of 1 vial (of either 2 ml or 5 ml of concentrate).

II.2 ACTIVE SUBSTANCE

rINN: Lecanemab

Chemical Name: Immunoglobulin G1, anti- (human β-amyloid protofibril) (human-Mus musculus monoclonal lecanemab heavy chain, disulfide with human-Mus musculus lecanemab light chain) dimer.

Molecular Formula: $C_{6644}H_{10248}N_{1748}O_{2108}S_{46}$ (protein with mature heavy chains and 2x G0F glycosylation)

Molecular Weight: ~150 kDa.

Chemical Structure: The amino acid sequence for lecanemab predicted from the DNA sequence is shown below:

Heavy Chain (HC):

Leader Sequence: MEWSWVFLFFLSVTTGVHS

```
EVQLVESGGG LVQPGGSLRL SCSASGFTFS SFGMHWVRQA PGKGLEWVAY  50
ISSGSSTIYY GDTVKGRFTI SRDNAKNSLF LQMSSLRAED TAVYYCAREG  100
GYYYGRSYYT MDYWGQGTTV TVSSASTKGP SVFPLAPSSK STSGGTAALG  150
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL  200
GTQTYICNVN HKPSNTKVDK RVEPKSCDKT HTCPPCPAPE LLGGPSVFLF  250
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE  300
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP  350
REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT  400
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL  450
SPGK                                                    454
```

Light chain (LC):

Leader Sequence: MSVPTQVLGL LLLWLTDARC

```
DVVMTQSPLS LPVTPGAPAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK  50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLRI SRVEAEDVGI YYCFQGSHVP  100
PTFGPGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK  150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE  200
VTHQGLSSPV TKSFNRGEC                                    219
```

Lecanemab is not the subject of a European Pharmacopoeia monograph.

Lecanemab is a recombinant monoclonal IgG1 antibody which targets amyloid beta peptide (Aβ). The antibody consists of two heavy chains (HC; γ1-chains), each of 454 amino acids, and two light chains (LC; κ-chains), each of 219 amino acids.

Lecanemab is manufactured using a recombinant CHO cell line.

The manufacturing process of the active substance has been adequately described and appropriate in-process controls and critical process parameters are applied.

Satisfactory specifications are in place for all starting materials and reagents.

Control of potential adventitious agents in the manufacture of lecanemab is assured through control of raw materials, in-process testing, viral clearance process validation, and facility controls. Master and Working cell banks are tested for the absence of microbial and non-microbial contaminating agents such as viruses, fungi and mycoplasma.

Sufficient characterisation data, including the structure and biological characteristics, have been supplied for the active substance. Impurities have been appropriately characterised and evaluated.

A suitable specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Reference standards have been adequately described and documented.

The primary packaging has been sufficiently described and has been shown to be suitable for its intended purpose.

Acceptable stability data have been generated supporting a suitable shelf-life when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process, including process controls. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months for the unopened vial, with the storage conditions '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' is acceptable.

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.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

The following non-clinical studies were submitted with this application:

- *In vitro* binding studies
- *In vitro* studies into the functional consequences of binding
- *In vitro* studies into the effect of lecanemab on preventing neuronal toxicity
- *In vitro* studies into the uptake of amyloid beta peptide by microglia
- *In vivo* pharmacology studies in different strains of transgenic mice
- Secondary pharmacology studies
- Pharmacokinetic studies
- Tissue cross reactivity studies
- Two single dose toxicity studies, one in rats and one in cynomolgus monkeys
- Two repeated dose general toxicity studies in cynomolgus monkeys
- A further safety study in transgenic mice
- A local tolerance study in cynomolgus monkeys

The tissue cross reactivity studies and general toxicity studies were conducted in accordance with current Good Laboratory Practice (GLP).

Please note that during its development, lecanemab was known as BAN2401 and so this may be referenced. Two other antibodies were also used, notably mAb158 which is a murine antibody and, less frequently, rec158, a murine allotype antibody.

III.2 Pharmacology

Primary Pharmacology

Lecanemab is a humanised antibody derived from the murine antibody mAb158. Binding properties of lecanemab and mAb158 to different amyloid beta forms were compared by ELISA-based methods. The amyloid beta forms were monomers (M), protofibrils (PF) and fibrils (F).

Study AD-TR-006

In this study, antibodies were incubated in solution with amyloid beta then added to wells coated with amyloid beta and after incubation, bound antibody was detected by alkaline phosphate-conjugated anti-mouse IgG/IgGM antibody with quantification of optical density after adding an enzyme substrate. This was done for different amyloid beta forms and higher affinity is shown by lower concentrations.

The study found that mAb158 bound to human amyloid beta and it had higher affinity for human amyloid beta protofibrils than amyloid beta monomers and fibrils. Lecanemab retained the amyloid beta binding properties of mAb158. It showed high affinity binding to amyloid beta protofibrils and low affinity binding to monomeric amyloid beta with IC50 values of 3 nM and 600 nM for these respective forms i.e. a 200-fold difference. mAb158 and lecanemab each had much higher affinity for amyloid beta protofibrils than for monomers (figure 1).

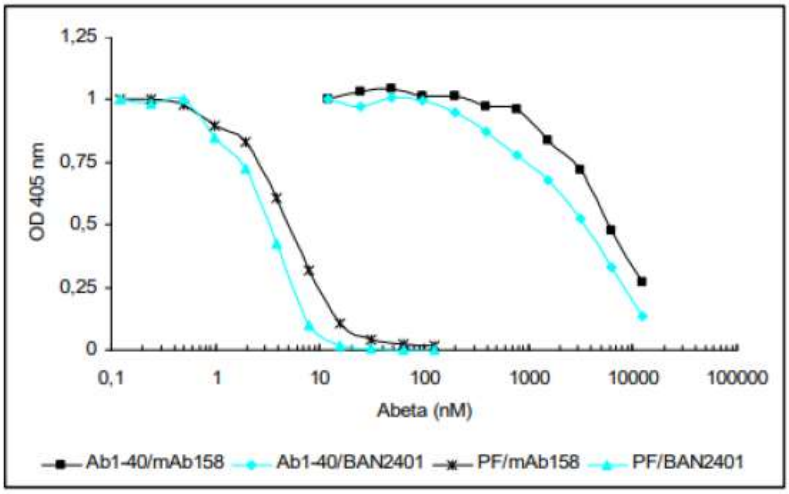


Figure 1. Lecanemab (BAN2401) and murine mAb158 analysed by competition ELISA

Binding of each of mAb158 and lecanemab to amyloid beta forms was also studied by surface plasmon resonance (SPR) analysis. The binding profiles as determined by surface plasmon resonance were the same as by ELISA: lecanemab and mAb158 each did bind protofibrils and monomers but binding to protofibrils was of notably higher affinity for each antibody than to monomers.

Study AD-TR-085

In study AD-TR-085, Fab regions were prepared from lecanemab and from mAb158 by pepsin digestion, purified and tested for binding to amyloid β protofibrils. ELISA-based methods were used and results were compared with those for binding of the full antibodies, mAb158 and lecanemab. In brief, this testing showed that Fab from mAb158 bound ~15-fold less efficiently to amyloid beta protofibrils as compared to the full mAb158 but that F(ab')2 from lecanemab binding was more-or-less equivalent to that of the full lecanemab antibody.

Study AD-TR-461

As well as soluble amyloid-beta aggregates comprising protofibrils and oligomers, the ApoE4 allele of apolipoprotein E is a risk factor for developing both Alzheimer's disease and for cerebral amyloid angiopathy. The molecular mechanism for the latter is not clear although it may be related to amyloid beta clearance.

In study AD-TR-461, the company measured amyloid beta protofibrils and their composition in brains from patients with Alzheimer's disease in comparison with such from aged-matched controls and investigated if these varied between different ApoE genotype. For this, soluble amyloid beta protofibrils were extracted from homogenised brain tissue (fresh frozen temporal cortex) of patients (n=24) and controls (non-dementia) (n=12), all of known ApoE genotype.

Amyloid beta 42 protofibrils were elevated in brain tissue from patients with Alzheimer's disease compared to controls. Concentrations of amyloid beta 42 protofibrils had a median value of 167.8 ng/g tissue in tissue from patients as compared to 1.7 ng/g tissue in controls. In protofibril fractions, there was ~40-fold higher concentrations of amyloid beta 42 as compared to amyloid beta 40.

The company concluded that these results confirmed that amyloid beta 42 protofibril concentrations in these brain extracts were found to be elevated in tissue from patients with

Alzheimer's disease as compared to controls. The concentrations correlated with pathologies and with different ApoE genotypes.

Study BR-035

In report BR-035, the epitope in amyloid beta to which lecanemab binds was described. The company studied the ability of lecanemab to bind to truncated peptide containing amino acids 1-16 and to peptides with sequential amino acid deletions from the amino terminus of the 1-16 sequence. Differential binding to the various deletion peptides indicates amino acids to which lecanemab binds.

Surface plasmon resonance methods were used. Binding of lecanemab to biotinylated versions of each amyloid beta peptide, from 1-16-LYS, 2-16-LYS and 3-16-LYS to 6-16-LYS was characterised and compared with that other antibodies:- firstly, 6E10 which is known to bind to amino acids 1-16 of amyloid beta with epitope within amino acids 3-8 and secondly, 4G8 which binds to amino acids 17-24 of amyloid beta; as a negative control an antibody that targets folate receptors was used. Table 1 summarises the peptides used.

Table 1. Peptide Identities and Sequences.

Peptide ID	Amino Terminal Modification	Aβ Amino Terminal Sequence (Residues 1–16)	Carboxy Terminal Sequence and Modifications
Peptide A	Biotin – LC -	DAEFRHDSGYEVHHQK	
Peptide B		DAEFRHDSGYEVHHQK	K (Biotin – LC) – NH2
Peptide C		AEFRHDSGYEVHHQK	K (Biotin – LC) – NH2
Peptide D		EFRHDSGYEVHHQK	K (Biotin – LC) – NH2
Peptide E		FRHDSGYEVHHQK	K (Biotin – LC) – NH2
Peptide F		RHDSGYEVHHQK	K (Biotin – LC) – NH2
Peptide G		HDSGYEVHHQK	K (Biotin – LC) – NH2
Peptide H	Biotin – LC -	DAEFRHDSGYEVHHQK	LVFFAEDVGSNKGAIIGLMVGGVVIA

Removal of the first 3 amino acids of amyloid beta 1-16 resulted in loss of lecanemab binding (<5% of binding to intact Aβ 1-16 (Peptide B)). By contrast, 6E10 antibody binding was not impacted until the first 5 amino acids are deleted; the negative control antibody did not bind to any of the amyloid beta peptides. Lecanemab's binding site is distinct from that of 6E10 as deletion of amino acid residues 2-3 removed lecanemab binding but not that of 6E10. The two amino acids, 2-3, (alanine, glutamate) of amyloid beta species represent an important linear epitope for lecanemab binding.

Study AD-TR-019

The purpose of study AD-TR-019 was to determine the binding affinity of lecanemab and of mAb158 to human and murine Fcγ receptor I (FcγRI); this was done using each of ELISA and surface plasmon resonance testing methods. Lecanemab (BAN2401) had ~12-16-fold lower affinity for murine Fc gamma RI as compared to mAb158 but bound equally to human Fc gamma RI. This was mainly due to a more rapid dissociation. Compared to interactions with murine Fc gamma RI, both antibodies dissociate more slowly from the human FcγRI. The company concluded that lecanemab and mAb158 had similar affinity for human Fc gamma RI but that lecanemab had lower affinity for murine FcγRI than mAb158.

Study AD-TR-058

Study AD-TR-058 reported binding to the human neonatal Fc receptor (hFcRn). IgG is normally internalised by endothelial cells and monocytes and escapes degradation by binding to FcRn at the acidic pH of the endosome. IgG is then recirculated to the blood and released

to the blood at neutral pH which results in a longer serum half-life. Interactions between the IgG and hFcRn are pH dependent: at pH 6 IgG binds to hFcRn, but at pH 7.4 it is released from the hFcRn. Testing should therefore use each pH, 6 and 7.4. Surface plasmon resonance methods were applied: hFcRn was immobilised on a sensor chip and exposed to various concentrations (0 – 8 microM) of test antibody, lecanemab. Sensorgrams for lecanemab (BAN2401) showed a fast association and dissociation during its interaction with hFcRn at pH 6 with a relatively high affinity binding showing a KD value of 0.6 µM. At pH 7.4, the interaction was notably different and an interaction described as specific but low was seen between hFcRn and lecanemab.

Study BR-034

In study BR-034, the company reported on development of assays using the biolayer interferometry (BLI) to measure the binding affinity of lecanemab for Fc gamma receptors: FcyRI, FcyRII and FcyRIII (CD 64, CD 32 b/c and CD 16 a/b respectively) and also to FcRn, the neonatal Fc receptor. The company concluded that these data showed that lecanemab bound to Fc gamma RI and Fc gamma RIII receptors but did not bind to Fc gamma RII receptors; lecanemab bound to mouse FcRn receptor; however, initial testing showed that lecanemab did not bind to human FcRn.

Study AD-TR-123

Report AD-TR-123 described the development of a potency assay based on lecanemab mediated uptake of amyloid beta protofibrils. A mouse microglial cell line, EOC-20, was used for this assay (lecanemab is also active at mouse Fc-gamma receptors): this is an immortalised microglial cell line derived from the brain of a normal mouse at age 10 days. Protofibril ingestion in microglia is mainly attributed to scavenger receptors but the formation of protofibril-antibody immune complexes redirects the uptake pathway through interactions with Fc gamma receptors. This report is considered as proof of the importance of Fc-receptor mediated uptake of lecanemab-bound amyloid beta protofibrils in microglial uptake of protofibrils.

Experiments were done with lecanemab alone and with lecanemab and an Fc gamma receptor blocker. 100 nM Aβ 1-42 protofibrils were used. Increasing amount of lecanemab (40-10,000 ng/ml) resulted in increased uptake of amyloid protofibrils into EOC-20 cells (figure 2). At 1000 ng/ml lecanemab, addition of Fc block was tested at concentrations of 0.5 pg/ml - 10 µg/ml. The testing was then repeated at Fc block concentrations of 2-5000 ng/ml. This resulted in a prominent sigmoidal dose-response curve with an EC50 of 40 ± 6 ng/ml (figure 3) with complete block at 186 ng/ml. From this, the company indicated that a concentration of 2.5 µg/ml Fc blocker should be sufficient to saturate the inhibition of Fc gamma receptor. The company concluded that lecanemab increases the amount of amyloid protofibrils ingested by EOC- 20 cells and does so through Fc gamma receptors.

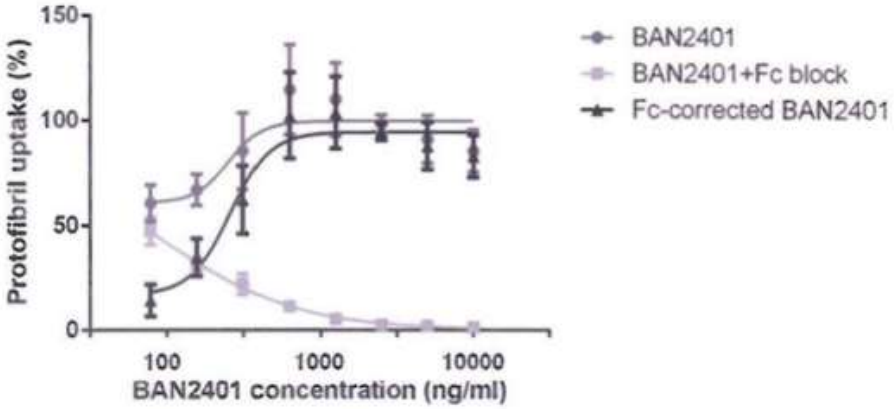


Figure 2. BAN2401 increases the amyloid protofibril uptake in EOC-20 cells in a concentration dependent manner.

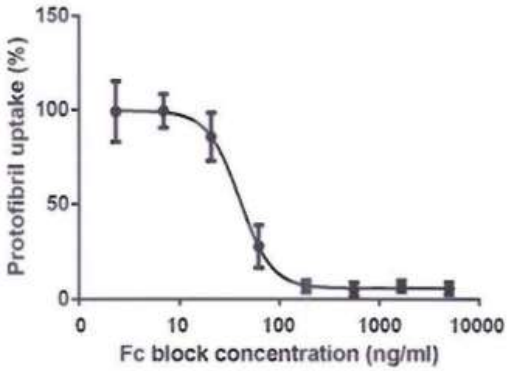


Figure 3. Fc block decreases the BAN2401 dependent amyloid protofibril uptake in EOC-20 cells in a concentration dependent manner

Study M22001

In report M22001, the company described the specificity of lecanemab for amyloid beta protofibrils. For this, the company purified each of amyloid beta protein 1-40 monomers and amyloid beta protein 1-42 protofibrils and, by ELISA-based methods, determined binding of lecanemab to each. As shown in Figure 4, there was a notably different binding profile of lecanemab with IC50 values for each of amyloid beta protein 1-40 monomer and amyloid beta protein 1-42 protofibrils of 27,000 nM and 3.6 nM, a difference of 7,500-fold. Lecanemab has higher affinity and therefore specificity for protofibrils as compared to monomer, the company concluded.

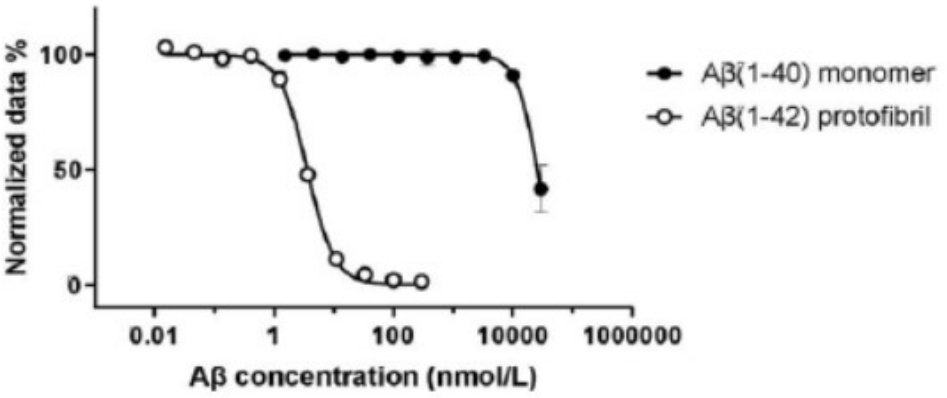


Figure 4. Inhibition ELISA with amyloid beta protein 1-40 monomer and amyloid beta protein 1-42 protofibrils

Study M22002
In report M22002, the company further described specificity of lecanemab for amyloid beta protofibrils. Binding of lecanemab to amyloid beta protein 1-40 monomers and amyloid beta protein 1-42 protofibrils was compared using surface plasmon resonance methods. Lecanemab again showed specificity for protofibrils with mean KD values for binding to monomers and to protofibrils of 1697.5 and 1.1618 nM, respectively. The company concluded that lecanemab has selectivity for protofibrils as compared to monomers.

Testing of binding of mAb158, the murine antibody, to amyloid beta monomers and protofibrils was also studied (report W-20090268). Using ELISA-based methods, its binding to each of amyloid beta low molecular weight oligomers (3-mers, low molecular weight of 14,768 Da), oligomers (6-mers, molecular weight not stated) and protofibrils (46-mers, high molecular weight of 207.586 Da) was described. mAb158 bound to amyloid beta protofibrils. It also bound to amyloid beta oligomers, but it did not bind to the low molecular weight amyloid beta monomers. Binding was thus dependent on the size of oligomers, the company concluded.

Further binding studies

- Ncl-1120: Binding studies of lecanemab and other Aβ binding antibodies to Aβ protofibrils in competition with monomers and fibrils. In this report, the company concluded that lecanemab, aducanumab and gantenerumab showed high selectivity for amyloid protofibrils as compared to monomers
- Study W-20220659: Characterization of Amyloid-beta – lecanemab interaction by HDX-MS. In this report the company concluded that lecanemab recognises the conformational epitope of the N-terminal and mid regions on amyloid beta (1-42) protofibrils and/or binds to the N-terminal region causing a structural change in the mid-region of amyloid beta (1-42) protofibrils.
- W-20210274: X-ray structure analysis of human anti-Aβ antibody (Lecanemab) Fab fragment in complex with Aβ peptide. This report detailed results of X-ray crystallography analyses of binding of the Fab region of lecanemab to amino acids 1-9 of amyloid beta peptide.
- m09007: Effects of BAN2401 on Amyloid β Protofibril Binding to Rat Primary Hippocampal Neurons in Culture. From this report, the company concluded that lecanemab decreased binding of amyloid beta protofibrils to rat primary hippocampal neurones.

Further studies relating to functional consequences of binding

- Study W-20090258: Effects of BAN2401 on Amyloid β Protofibril Binding to Dendritic Spines in Rat Primary Hippocampal Neuron Culture. This report concluded that lecanemab and mAb158 each inhibited amyloid beta protofibril binding to dendritic spines of hippocampal neurones
- Study W-20090273. ABBA: in vitro Inhibition of beta-sheet formation. This report concluded that lecanemab and mAb158 each inhibited beta sheet formation of amyloid beta
- Co16640: 1. Optimization experiments to obtain correct stoichiometry of BAN2401 and Abeta aggregates 2. Effect of BAN2401on Abeta aggregates 3. Effects of BAN2401-Abeta adducts in an ex-vivo assay using hippocampal slices for LTP measurement using Multi Electrode Array (MEA) for electrophysiology. This report concluded that lecanemab influences the aggregation of amyloid beta peptide and has

protective effects against amyloid beta 1-42-induced impairment of long-term potentiation (LTP). LTP is a process, detectable by electrophysiological means which, in the hippocampus, is thought to be a mechanism for establishing new memories.

Studies showing the effects of lecanemab on neuronal toxicity due to amyloid beta 1-42.
Amyloid beta 1-42 is proposed as a specific neurotoxic agent causing the degeneration of neuronal tissue that is a specific hallmark of Alzheimer's disease, as compared to other types of dementia.

Study M09010
In study M09010, rat primary medial septum neurones, sourced from embryos aged 18.5 days old, in culture were exposed to lecanemab and thereafter, amyloid beta 1-42 protofibrils were added. Cells were plated at 1.2x10(5) cells per well and cultures were maintained for 2 days then the degree of neuronal toxicity was determined based on measurement of lactate dehydrogenase (LDH) activity in the supernatant. The basis of this assay is that activity of this enzyme in the supernatant will increase if cells die, this tests the capacity of lecanemab to prevent neuronal toxicity arising from exposure of neurones to amyloid beta 1-42.

Lecanemab did not inhibit amyloid beta protofibril-induced neuronal cell toxicity at concentrations from 50 - 1000 µg/ml (Table 2).

Table 2. Effect of lecanemab on amyloid beta 1-42 protofibril - induced cell toxicity.

Treatment	LDH release (%)
NaOH/PBS + PBS	5.5±0.3
5.5 µmol/L Aβ PF + PBS	11.6±0.6
5.5 µmol/L Aβ PF + BAN2401 50 µg/mL	10.9±0.8
5.5 µmol/L Aβ PF + BAN2401 150 µg/mL	11.1±0.6
5.5 µmol/L Aβ PF + BAN2401 750 µg/mL	11.9±0.5
5.5 µmol/L Aβ PF + BAN2401 1000 µg/mL	12.4±0.9
5.5 µmol/L Aβ PF + IgG1 1000 µg/mL	12.4±0.1

The company concluded that lecanemab did not inhibit amyloid beta protofibril-induced neuronal toxicity.

Study W20090274
The aim of this study was to describe the effect of lecanemab and of mAb158 on neuronal toxicity induced by amyloid beta 1-42.

For this testing the company used rat primary medial septum neurones in culture. These were exposed to lecanemab or to mAb158, or to controls of a non-specific human IgG1 or a mouse IgG2a. Saline was used as a negative control. After 1 hour incubation of cells with the test antibody (concentration range) amyloid beta 1-42 oligomers or protofibrils were added (or as a control 1% dimethyl sulfoxide was added). Culture plates were maintained for 2 days further, and then neuronal toxicity was quantified, by means of testing the supernatant for lactate dehydrogenase (LDH): a reduction in LDH concentrations is proportional to neutralising activity. Maximal release of LDH was determined (using testing with pyruvate) and results expressed in term of % this maximal value.

Experiments tested the effect of (1) mAb158 and lecanemab on amyloid beta protofibril-induced neuronal cell toxicity and (2) and (3) the effect of mAb158 and of lecanemab on amyloid beta oligomer-induced neuronal cell toxicity.

Amyloid beta protofibrils lead to an increase in LDH release of 21.4% of the maximal value, compared to 9.4% for the control, exposed only to saline. Similarly, comparing rows 1 and 4 of Table 4 and rows 1 and 4 of Table 5 indicates a similar neurotoxic effect of amyloid beta oligomers, with an increase in LDH to 22.0% of the maximal value compared to 5.2% for the controls in Table 4 and an increase in LDH to 16.3% of the maximal value compared to 5.9% for the controls in Table 5.

In test (1), lecanemab reduced the LDH concentration in neurones exposed to amyloid beta protofibrils at 100 and 300 µg/ml (Table 3): mAb158 at 100 µg/ml also reduced LDH (Table 3). The reduction in LDH release is interpreted as a reduction in neurotoxicity.

In tests (3) and (2) lecanemab also inhibited amyloid beta oligomer-induced neuronal toxicity and did so at concentrations lower than 100 µg/ml (Table 5); mAb158 also inhibited amyloid beta oligomer-induced neuronal toxicity at 100 µg/ml (Table 4).

Table 3. Effect of mAb158 and lecanemab on amyloid beta protofibril-induced neuronal cell toxicity

Treatment		% of LDH release
blank	PBS + PBS	9.4 ± 0.8
control	3 µmol/L Aβ PF + PBS	21.4 ± 0.5
	3 µmol/L Aβ PF + IgG1 100 µg/mL	19.7 ± 1.0
	3 µmol/L Aβ PF + IgG1 300 µg/mL	20.0 ± 1.0
	3 µmol/L Aβ PF + BAN2401 100 µg/mL	13.3 ± 1.0
	3 µmol/L Aβ PF + BAN2401 300 µg/mL	9.5 ± 0.5
	3 µmol/L Aβ PF + IgG2a 100 µg/mL	15.3 ± 0.5
	3 µmol/L Aβ PF + mAb158 100 µg/mL	10.7 ± 0.4

Values are represented as mean±SEM of 3 or 4 wells.

Table 4. Effect of mAb158 on amyloid beta oligomer-induced neuronal cell toxicity

Treatment		% of LDH release
blank	PBS containing 1% DMSO + PBS	5.2 ± 0.2
	PBS containing 1% DMSO + IgG2a 100 µg/mL	6.0 ± 0.3
	PBS containing 1% DMSO + mAb158 100 µg/mL	5.7 ± 0.2
control	4 µmol/L Aβ oligomer + PBS	22.0 ± 2.4
	4 µmol/L Aβ oligomer + IgG2a 100 µg/mL	23.3 ± 0.7
	4 µmol/L Aβ oligomer + mAb158 100 µg/mL	19.3 ± 0.3

Values are represented as mean±SEM of 3 wells.

Table 5. Effect of lecanemab on amyloid beta oligomer-induced neuronal cell toxicity

Treatment		% of LDH release
blank	PBS containing 1% DMSO + PBS	5.9 ± 0.3
	PBS containing 1% DMSO + IgG1 100 µg/mL	6.0 ± 0.5
	PBS containing 1% DMSO + BAN2401 100 µg/mL	6.0 ± 0.3
control	5 µmol/L Aβ oligomer + PBS	16.3 ± 0.6
	5 µmol/L Aβ oligomer + IgG2a 100 µg/mL	16.2 ± 0.7
	5 µmol/L Aβ oligomer + BAN2401 100 µg/mL	8.8 ± 0.4
	5 µmol/L Aβ oligomer + BAN2401 80 µg/mL	14.1 ± 0.2
	5 µmol/L Aβ oligomer + BAN2401 60 µg/mL	14.5 ± 0.7
	5 µmol/L Aβ oligomer + BAN2401 40 µg/mL	13.4 ± 0.5
	5 µmol/L Aβ oligomer + BAN2401 20 µg/mL	16.9 ± 1.2

Values are represented as mean±SEM of 4 wells.

The company concluded that both mAb158 and lecanemab inhibited amyloid beta protofibril-induced neuronal toxicity *in vitro* albeit at high concentrations. They also inhibited amyloid beta oligomer-induced neuronal toxicity at high concentrations.

Study CO18660

This study examined the potential for cellular toxicity induced by amyloid beta 1-42 to be prevented by lecanemab. This testing was done in SHSY-5Y cells in culture, at passage 45 – these cells were derived from an original cell line that was sourced from a patient with neuroblastoma. Testing was also done in primary cortical neurones derived from chicken embryos aged 8 days old.

Cultured cells were exposed to amyloid beta 1-42 either alone or with lecanemab (concentration range of 0.01-3 microM) added to the cells prior to addition of amyloid beta 1-42 and cell viability was determined by an MTT assay, which measures cellular metabolic activity by colourimetric means.

For primary chicken neurones and for cells of human neuroblastoma origin, cytotoxicity was induced by amyloid beta 1-42 peptide, used at a concentration of 3 microM. Lecanemab produced a reduction in the degree of cytotoxicity induced by 3 microM amyloid beta 1-42, with a no effect concentration determined at 0.03 microM lecanemab (in primary chicken neurones) and 1 microM (in SHSY-5Y cells). When cells were exposed only to lecanemab, 3 microM, cell viability was slightly reduced.

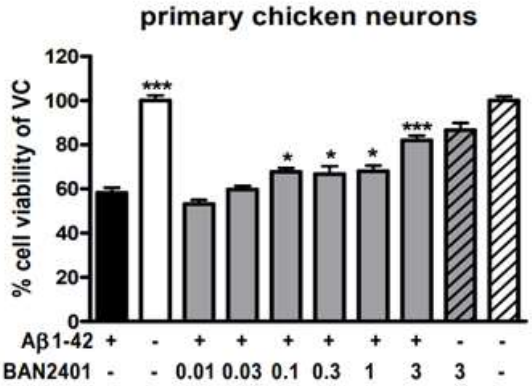


Figure 5. Effects of BAN2401 on amyloid beta 1-42 induced toxicity in primary chicken neurons

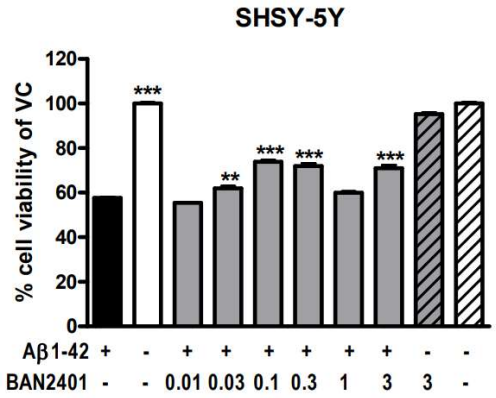


Figure 6. Effects of BAN2401 on amyloid beta 1-42 induced toxicity in SHSY-5Y cells

Report LMS-0432-02-26207

A series of experiments were presented into uptake of amyloid beta peptide by microglia. The process of removing microglia from their native brain environment and placing them into artificial culture conditions appears itself to lead to microglial activation. Under these conditions, microglia from both patients and controls are likely to be highly activated. The experiment assessed if there was a difference in microglial uptake of amyloid beta protofibrils when comparing between cells sourced from patients with Alzheimer's disease and elderly controls.

For this, microglial cell cultures, plated at 3x10(5) cells/well were incubated for 12 hours with amyloid beta protofibrils at concentrations of 0, 100, 500, 1000 or 2000 pg/ml. After incubation, 6E10, an antibody to amyloid beta was added, as was DAPI, which shows nuclei, and the cells were visualised.

The protofibrils were taken up by microglial cells in a concentration-dependent manner by both patient and control samples. However, in controls uptake was more diffuse, whereas in patient samples, there was localisation to phagosomes.

The experiments then assessed whether opsonisation of protofibrils by lecanemab enhances protofibril uptake and cytokine secretion. For this, protofibrils (168 pM) were exposed for 15 minutes to lecanemab (0, 56, 112, 168 or 224 pM) and this mix was then added to plated microglial cells (3x10(5) cells/well) sourced from either patients with Alzheimer's disease or elderly controls; from other wells, the supernatant was retrieved and stored for later analysis for cytokine concentrations.

Uptake of opsonised protofibrils appeared to increase with lecanemab. As before, in cultures of cells from patients, uptake of lecanemab-opsonised protofibrils appeared to be localised to phagosomes.

With increased protofibril uptake, there was a reduction in the overall inflammatory cytokine profile: 23 of the 38 inflammatory proteins tested exhibited a significant, positive dose response to graded concentrations of lecanemab-opsonised protofibrils. Of these, the most significant were IL-1ra ($R = 0.441$, $P < 0.01$), TIMP-1 ($R = 0.507$, $P < 0.01$), RANTES ($R = 0.509$, $P < 0.01$), MCSF ($R = 0.540$, $P < 0.001$), and I-309 ($R = 0.565$, $P < 0.001$). Three cytokines showed exceptionally high correlations: TNF-α, IL-1β, and IL-6. All three are

increased in AD cortex. However, there was no difference between cultures from patients with Alzheimer's disease as compared to controls: this was also found for comparisons when all individual cytokines were analysed.

The experiments then examined if lecanemab enhances protofibril uptake by opsonising protofibrils and engaging an additional Fc-mediated pathway for microglial phagocytosis. For this, a culture of microglia from patients with Alzheimer's disease was tested with 1000 pg/ml protofibrils alone or with 1000 pg/ml protofibrils that had been pre-incubated with lecanemab at an equimolar concentration, in the presence or absence of a 50% solution of Fc Receptor Blocker.

Lecanemab increased amyloid beta amyloid beta uptake by microglia whereas blockade of Fc receptors reduced protofibril uptake by 90% when lecanemab was present; in the absence of lecanemab, the Fc blocker had almost no effect. The company concluded that lecanemab enhances microglial uptake of protofibrils by engaging an Fc-mediated pathway for phagocytosis.

***In vivo* pharmacology**

In vivo pharmacology studies were performed in different strains of transgenic mice with deficits associated with amyloid deposition. The majority of studies were done in Tg2576 mice which overexpress a mutant form of amyloid precursor protein (APP) and develop amyloid plaques and progressive cognitive deficits. Some studies were also done in Tg-APP ArcSwe mice, which carry the APP gene with both the Swedish (K670N/M671L) and Arctic (APPE693G) mutations; they develop amyloid plaques. Finally, one study was done in AppNL-G-Fknock-in mice which express pathogenic amounts of amyloid beta protein consequent upon the effects of three mutations associated with familial Alzheimer's disease.

Studies in Tg2576 mice

Study Nsea2013-025

mAb158 is a mouse monoclonal antibody against amyloid β (Aβ) protofibril of IgG allotype IgG2a (IgG2aa): as this was highly immunogenic when given to Tg2576, the company considered that a different allotype antibody might be less immunogenic and so created such a different antibody, called recombinant (rec) 158, which is of IgG allotype IgG2c (IgG2ab). In this study immunogenicity of the two antibodies was tested in Tg2576 mice and any impact on kinetics of any immunogenic response was investigated.

Eight or 9 female mice of age 9 months of strain Tg2576 (C57BL/6;SJL-Tg(APPSWE) 2576Kha/rd1) and non-transgenic littermates were used in this study. They were given mab158 or rec158 at 20 mg/kg intraperitoneally: dosing was once weekly for 8 weeks. ~100 microlitres of blood was drawn from tail veins before dosing and at 24, 72, and 168 hours after the 1st and 8th injections and exposure to mAb158 and rec158 was quantified. Antibody to each of mAb158 and rec158 levels were measured in plasma from blood samples taken weekly just prior to each injection and also at day 7 after the last (8th) dose. Mice were then killed, and brains prepared for analyses of brain protofibril concentrations.

ELISA methods were applied to determine each of mAb158 and rec158; antibody to each of these was determined by SPR (surface plasmon resonance) methods (Biacore). Amyloid levels in the brains of control- and antibodies-treated mice were measured using 6E10 staining. Microglia involvement in the immunotherapy was assessed by Iba1 staining. Quantification of diffuse plaque load and microglia was reported as area fraction (% area),

defined as the area positive for the staining over the total area analysed. Amyloid beta protofibril was measured by sandwich ELISA.

Exposures were higher in mice given mAb158 than rec158: this difference was statistically significant. Antibodies to mAb158 and rec158 were more frequent in mice given rec158 as compared to mice given mAb158.

As indicated by quantification of 6E10-positive amyloid plaques in the brains, there was a significant decrease in mice given mAb158, both in the cortex and in the hippocampus but there was no such reduction in mice given rec158-treated animals.

Quantification of Iba1-positive microglia in the brain of Tg2576 detected a significant decrease in mice given mab158, both in the cortex and in the hippocampus. In the cortex, also mice given rec158 showed less Iba1-positive staining than wild-type and Tg2576 vehicle-treated mice.

Brain protofibril were not reduced in mice given either mAb158 or rec158.

The company concluded that mAb158 showed higher plasma concentration and lower ADA induction, compared with rec158 and that mab158 reduced diffuse plaque load in the hippocampus and cortex in Tg2576 mice while rec158 did not. Neither showed a significant reduction of brain protofibril.

Study W20090269
In study W20090269, the company sought to test immunogenicity of lecanemab in older Tg2576 mice. Twelve female Tg2576 mice, aged 17 months, were given intraperitoneal doses of lecanemab once daily for 14 days at doses of 0 or 24 mg/kg: the control was a human IgG1; a further group were given saline. 24 hours after the last dose, blood was collected under anaesthesia and plasma prepared and used for analysis of mouse anti-human immunoglobulin responses (IgG and IgM) by ELISA. The study found that all the mice given lecanemab developed antibodies as did all mice given the control human IgG1: anti-human IgG antibodies (mouse IgG and IgM isotypes) were detected in 1000-fold diluted plasma of mice given each of the test and control antibodies but not in mice given saline.

Study W-20090278
In this study female Tg2576 mice (n=6/group; 14 months old) were dosed intraperitoneally once weekly with mAb158 at 0 or 24 mg/kg for 1, 2 or 4 weeks and killed 1 week after the last dose. The concentration of amyloid beta protofibrils/oligomers and of mAb158 in the brain were each measured. In mice given the antibody, after 1 week, there was no change in amyloid beta protofibrils/oligomers but after 2-4 weeks, these were reduced by 27-28%.

Study W-20100295
In this study female Tg2576 mice (n=10/group; 20 months old) were dosed intraperitoneally once weekly for 4 weeks with mAb158 at 0 or 24 mg/kg. At the end of the dosing period, ciriculating antibody to mAb158 did not differ between these two groups of mice; in mice given mAb158, amyloid beta protofibrils and soluble amyloid beta (x-42) concentrations were decreased by 30% in brain tissues.

Study W-20090277
In this study female Tg2576 mice (n=15/group; 4 months old) were dosed intraperitoneally once weekly for 4 months with mAb158 at 0, 3, 6 or 12 mg/kg and were killed 5 days after

the last dose. Brain and cerebrospinal fluid concentrations of amyloid beta protofibrils were decreased in a dose-dependent manner by 15-17% and 20-48% at the doses of 6 and 12 mg/kg respectively.

The following studies on Tg2576 mice were also submitted :

- Nsea2014-015 ABBA: A behavioral study by treatment of mAb158, antiamyloid-β protofibril antibody, in Tg2576
- Study W-20090276 ABBA mAb158: Effects on brain Aβ protofibrils/oligomers, Aβ plaques, Aβx-42 and Aβx-40 in 12.5-month-old Tg2576 mice
- Ncl-1065 : Time course study to evaluate the effects of mAb158 on amyloid-beta protofibril levels and plaque load in aged female Tg2576 mice following treatment for 18 weeks and after an off-treatment period
- Study AD-TR-443 : Time course study to evaluate the effects of mAb158 on amyloid-P protofibril levels and plaque load in aged female Tg2576 mice
- BIOMA-2012-056 :A longitudinal multimodal imaging study of the effect of mAB158 on brain function in aged Tg2576

Studies in AppArc/Swe mice

Study AD-TR-008

Wild type or $App_{Arc/Swe}$ mice were dosed with mAb158 at 0 or 10 mg/kg either intraperitoneally once a week for 4 weeks or intravenously once a day for 4 days (n=7 [5M, 2F]/group). There was no reduction in amyloid protofibril concentrations in the brains of mice dosed intravenously; however, in the brains of mice dosed intraperirtoneally, there was a reduction of 30% compared to controls not given mAb158.

Study AD-TR-010

Wild type or $App_{Arc/Swe}$ mice, aged 9-16 months (n=6/1-2F, 4-5M), were dosed with mAb158 at 0, 1, 3 or 10 mg/kg intraperitoneally once a week for 4 weeks and killed 1 week after the last dose. Brain concentrations of mAb158 increased with dose (3.6, 9.8, 20.3 ng/ml at doses of 1, 3 and 10 mg/kg); brain concentrations of amyloid beta decreased with dose with decreases relative to controls of 25, 59 and 69% respectively.

Study AD-TR-014

$App_{Arc/Swe}$ mice, aged 11 months (n=7/group gender not stated), were dosed with mAb158 at 0 or 10 mg/kg intraperitoneally once a week for 4 weeks and killed either 24 hours or 1 week after the last dose. Concentrations of mAb158 in the brain, cerebriospinal fluid and plasma were lower in mice killed at day 7 compared to in those killed 24 hours after the last dose, although the differences were not statistically significant. Brain and cerebrospinal fluid concentrations of protofibril decreased in mice given the antibody (brain: 34-35% reduction; cerebrospional fluid: 61-74% reduction).

Study AD-TR-007

$App_{Arc/Swe}$ mice, aged 9-10 months (n=4F and 6M/group), were dosed with mAb158 at 0 or 12 mg/kg intraperitoneally once a week for 18 weeks and killed 1-3 days after the last dose. Concentrations of amyloid beta protofibrils in brain were reduced 80% in mice given mAb158 compared to controls; however, there was no difference in brain concentrations of soluble amyloid beta, insoluble amyloid beta, plaques or phosphorylated Tau.

Study AD-TR-011
App$_{Arc/Swe}$ mice, aged 12-14 months (n=4-5F and 4-5M/group), were dosed with mAb158 at 0, 0.3, 1, 3 or 10 mg/kg intraperitoneally once a week for 4 months and killed 7 days after the last dose and brain and cerebrospinal fluid concentrations of mAb158 were determined. These increased but not in proportion with dose with values for brain of 1.8, 2.8, 4.3 and 5.7 ng/ml for dose groups 0.3, 1, 3 and 10 mg/kg respectively and values for cerebrospinal fluid of 27, 102, 493 and 1300 ng/ml also respectively. Brain, but not cerebrospinal fluid concentrations of amyloid beta protofibril were reduced compared to the control group (28, 33, 54 and 50%). There was no change in concentrations of total amyloid beta 40, total amyloid beta 42, soluble amyloid beta 40, or soluble amyloid beta 42 in either the brain of cerebrospinal fluid. There were no histopathological findings in the liver, kidneys, heart, lung, spleen, stomach, small itesting, large intestine or lymph nodes.

Study W-2010-0159
*A*ppArc/Swe mice, aged 4 months (n=15F) were dosed with mAb158 at 0, 3, 6, or 12 mg/kg intraperitoneally once a week for 18 weeks. From the 16th dose, mice were assessed in contextual and auditory-cued fear conditioning memory tests. There was no significant difference in performance in either test; however, in the auditory-cued test there was a slight increase in the measure of performance at each of 6 and 12 mg/kg.

The following reports from studies on Tg-APP ARcSwe mice were also submitted :

- Study AD-TR-055 SEC04: Short term efficacy of rec158 in tg-APP ArcSwe mice shown by 82El-MSD assay.
- Study AD-TR-070 B1008: Mass spectrometry analysis of different Aβ species in CSF from tg-APP ArcSwe mice after mAb158 treatment.
- Study AD-TR-009 : Long-term efficacy of mAb158 in old Tg-APP ArcSwe mice.

The following report from studies on AppNL-G-Fknock-in mice was also submitted :

- m20003 : Effects of 16 weeks treatment of mAb158 on Aβ protofibrils, TBS-insoluble Aβ levels and Aβ plaque in brain of AppNL-G-Fknock-in mice.

Secondary Pharmacology
In silico analyses were undertaken (study AD-tr-0117) to try to identify peptides binding to human MHC class II and to known helper CD4+ T cell epitopes.

The method was based on comparison of overlapping peptides (9-mers) from the variable regions of lecanemab with high affinity binders to human MHC Class II which are thought to correlate with T cell epitopes which could elicit T cell responses.

From this study, the company concluded that this analysis identified peptides in lecanemab that are predicted to bind to human MHC class II and/or share homology to known T cell epitopes. These sequences contain a total of 7 promiscuous high affinity and 5 promiscuous moderate affinity MHC class I binding peptides. Two partial matches to previously identified T cell epitopes were also identified and were considered to have a risk of being T cell epitopes and so associated with a significant risk of immunogenicity. The company note that this methodology tends to overpredict immunogenic potential as it does not account for other factors such as antigen processing or T cell tolerance.

The following secondary pharmacology studies were also submitted :

- W20090269 ABBA: Immunogenicity of BAN2401 antibody

- AD0TR-060 : Identification of BAN2401-binding plasma proteins
- AD-TR-0145 : Antitope Episcreen Immunogenicity Analysis of BAN2401
- BIOMT02012-01 BAN2401: An Integrated Summary of Studies Investigating the Potential Interaction of BAN2401 with Multiple Proteins

Of particular note, the AD-TR-060 report above recorded that a sequence with similarities to the linear amyloid beta epitope of lecanemab was identified in the thrombospondin (THBS-1) sequence and binding to this sequence was confirmed. Amyloid beta and thrombospondin-1 seem to compete for the same binding site on lecanemab. Lecanemab, mAb158 and rec158 all bind to thrombospondin; however, in quantitative considerations of the affinity (~4 microM) and of plasma concentrations of lecanemab in humans (50-250 ng/ml) , the company concluded that this off-target binding probably does not explain the short half-life of the antibody in man. This binding implies a potential for concern over clotting; the general toxicity studies did not identify this as of toxicological relevance.

Safety pharmacology
Separate safety pharmacology studies were not performed; relevant evaluations of effects on vital systems were made in general toxicology studies.

Pharmacodynamic drug interactions
Pharmacodynamic drug-drug interaction studies were not performed.

Overall conclusions on pharmacology
Alzheimer's disease (AD) is a neurodegenerative condition with progressive decline in cognitive function. The cause of this is linked to the accumulation in the patient's brain of amyloid beta proteins (Aβ) that form structures of plaques and neurofibrillary tangles that are toxic to neurones. Disease may present with mild cognitive impairment with progression to dementia – progression has been related to the presence of brain amyloid and the theory has developed from this that removal of amyloid beta may be a means of treating Alzheimer's disease, or of preventing the patient's decline.

Lecanemab is a humanised antibody that binds to amyloid beta protofibrils and less potently to amyloid beta monomers. In theory, by this binding, lecanemab directs phagocytic cells to remove lecanemab-bound soluble amyloid beta and derivatives leading to reduced brain amyloid, so reducing amyloid associated neurotoxicity; preservation of neurones hinders worsening of the patient's condition.

To support this theory, the company showed that both lecanemab and the surrogate murine antibody mAb158, preferentially bound amyloid beta protofibrils with IC50 values in in vitro systems in the low nanomolar concentration range: by contrast, although it did bind to amyloid beta monomers, it only did so with IC50 values that were much (>1000-fold) higher.

The company applied testing with surface plasmon resonance to describe the nature of engagement between lecanemab with amyloid beta protofibrils and monomers. This indicated that lecanemab associated faster with, and dissociated slower from, protofibrils as compared to monomers, indicating the higher selectivity for protofibrils than for monomers. This reflects the action of the Fab region of lecanemab.

To determine where in amyloid beta lecanemab bound, the company created different forms of amyloid beta by sequential removal of its N-terminal amino acids and tested if binding to

lecanemab was retained. This indicated that N-terminal amino acids 2 to 3 of amyloid beta species is a target for lecanemab binding.

In a screen for potential crossreactivity, lecanemab was found to bind to thrombospondin-1 although it did so much less potently than to its primary target and the company argue that, based on quantitative comparisons, *in vivo* binding in humans is likely to be minimal. This binding may have arisen from sequence similarities in a region of thrombospondin-1 with amyloid beta. A suspected role of thrombospondin-1 is in platelet activation: it is not clear whether there is the same binding of lecamenab to thrombospondin-1 from monkeys or whether mAb158 might bind to murine thrombospondin-1 but in the toxicity studies, no effect on platelet function or bleeding was identified.

The potential for off-target binding was explored by identification of lecanemab-interacting proteins in the plasma from rat, mouse, cynomolgus monkey, healthy human subjects, and AD subjects as detected by immunoprecipitation followed by western blot analysis. A 150 kDa band was immunoprecipitated from all samples analysed, and the 150 kDa band from human plasma was identified as thrombospondin-1 (THBS1) by mass spectrometry. The amino acid sequence homology of THBS1 between human and cynomolgus monkey or human and murine is known to be high (99.23% or 94.70%, respectively), and lecanemab is likely to bind to monkey or murine plasma THBS1, although the 150 kDa proteins detected in samples in these animals were not identified.

It seems likely that the lack of effect on bleeding in monkeys is not because lecanemab did not engage thrombospondin. The data implies the possibility that lecanemab did bind thrombospondin-1 in monkeys and did not cause bleeding. As the monkeys were healthy, the studies in monkeys do not take account of a possible interaction between disease pathology and thrombospondin-1 interactions. The explanation for why some people, very notably a minority, develop bleeding on treatment with lecanemab should be sought from studies in humans.

The company also described Fc binding properties of lecanemab. It had high affinity for human Fc gamma receptors (I and III). This links to its presumed mode of action. The company presented data that once bound to its target amyloid beta protein, lecanemab enhanced microglial cell uptake of amyloid beta and this was dependent on Fc receptor engagement: the drug acts by antibody-dependent cell-mediated phagocytosis (ADCP) to remove amyloid beta.

The functional consequence of lecanemab was tested and data showed that the neurotoxic effect of amyloid beta species was prevented by the presence of lecanemab in each of primary cortical neurones from chickens and also in cultured human neuroblastoma cells. In essence, this points to two modes of action of lecanemab, one being the binding mediated by its Fab regions which blocks the effect of amyloid beta on neuronal tissue and the second being removal of amyloid-beta bound to lecanemab by ADCP as described above.

As the target of lecanemab is soluble rather than membrane-bound, there is less concern for Fc-mediated effects by antibody-dependent-cellular cytotoxicity and complement-mediated cytotoxicity. There was no evidence of T cell activation-type effects in the studies reviewed.

Lecanemab and mAb158 also inhibit amyloid beta aggregation. This information was not reviewed in this assessment.

An effect of lecanemab to inhibit impediment in long-term potentiation (LTP) was shown in hippocampal tissue. LTP is a synaptic process that can be observed by electrophysiological means which occurs during new memory formation. Amyloid beta produces a reduction in LTP which was prevented by lecanemab: this provides evidence that lecanemab might be able to improve new memory formation, a key issue in this patient population.

In vivo, lecanemab was immunogenic when given to mice and so murine surrogate antibodies, mAb158 and an allotype-variant murine homologous recombinant protein of mAb158 rec158, were developed for *in vivo* testing in mice.

In vivo testing was done in transgenic mice with abnormalities leading to excess production of amyloid beta in their brains. Dosing with the murine antibody, mAb158 lead to reductions in brain amyloid beta protofibrils with activity seen in the dose range 0.3 - 50 mg/kg. This was sustained in the longer term (e.g. in studies with dosing over 18 weeks) and was also associated with, in some instances, a reduction in brain plaque content. A divergence of effects, to reduce diffuse plaques but not to reduce core plaques was suggested.

These data prove the intended effect of lecanemab to reduce amyloid beta in the brains of transgenic mice predisposed to develop high levels of amyloid in brain tissue. However, from the *in vivo* studies, there was no evidence presented to indicate that treatment of mice with mAb158 lead to improvement in cognitive function.

III.3 Pharmacokinetics

The following pharmacokinetic studies were submitted:

- 6 method validation studies (ELISA and ECL) and two long-term storage stability studies
- 4 absorption studies carried out in mice and monkeys.
- 1 distribution study in mice

III.4 Toxicology

Toxicity studies were performed in rats and cynomolgus monkeys.

Tissue cross reactivity studies

Binding to tissues from rats, cynomolgus monkeys and from humans was studied. The conclusions as summarised below were from studies in compliance with Good Laboratory Practice.

In study S09058, lecanemab bound to sections of aged Tg2576 mouse brain and did not bind to non-target tissue (rat and monkey thigh muscle). This, with lack of reactivity of the negative control antibody, indicated that the assay was sensitive, specific and reproducible.

There was no cross-reactivity of lecanemab to the panel of rat tissues used. Specific binding of lecanemab was identified in cynomolgus monkey tissues of the central nervous system of pia mater and subpial/perivascular space (cerebrum, cerebellum and spinal cord). Staining in the cytoplasm was also noted in endocrine cells in the pituitary and proximal tubular epithelial cells of the kidney.

In studies in human tissues (IM1533 and IM1599), to confirm the suitability of methods, studies were initially done with brain tissues from patients who had had Alzheimer's disease. The main study was done in healthy tissues, sourced from at least three donors: lecanemab was tested at 5 and 25 microg/ml.

Lecanemab produced strong to intense staining of the positive control tissue (brain from patients with Alzheimer's disease) at both concentrations examined but did not bind to the negative control (normal human striated skeletal muscle) at either concentration examined. The negative control antibody did not bind to either tissue. The study was judged to be reliable.

Lecanemab-specific bind was identified to the following human tissues:
- extracellular (presumed amyloid) plaques in the cerebrum
- neurones of the cerebrum and cerebellum
- glial cells of the cerebru, cerebellum and spinal cord
- retina
- ganglia
- adrenal gland
- salivary gland (acini and ducts)
- myenteric plexi, gastrointestinal tract – colon (large intestine), oesophagus and small intestine
- endocrine cells of the pituitary neurohypophysis
- epithelia of the adrenal cortex, large intestine (colon), oesophagus and small intestine, kidney, proximal tubules, hepatocytes, pancreatic acini
- placental trophoblasts
- testis (spermatogenic cells and Sertoli cells)
- thyroid follicles
- ureter
- uterus – body (endometrium)

  and also mononuclear cells in several organs (e.g. Fallopian tube, colon, small intestine, lung, lymph node, tonsil and the islet cells of the pancreas.

Staining of lecanemab in neurones, as well as staining of epithelium, mononuclear cells, and islet cells were observed within the cytoplasm (perinuclear in neurons) and in cytoplasmic granules.

The company concluded that lecanemab reacted with extracellular amyloid β plaques in cerebrum, neurones and glial cells, epithelium and mononuclear cells in some organs/tissues and pancreatic islet cells. Binding with extracellular amyloid beta protein was expected and there was no membranal staining. However, binding in neurones, mononuclear cells and islet cells was unexpected: this might represent binding to amyloid-protofibril-like or other cross-reactive material. Binding in pancreatic tissue might represent binding to islet amyloid polypeptide (IPP). Intracellular staining is not considered to be of *in vivo* significance as the antibody does not access the cytoplasm.

Single dose toxicity

Two single dose general toxicity studies were performed, one in rats (S09060) and one in cynomolgus monkeys (S09019): both were in compliance with Good Laboratory Practice.

In groups of 5 male and 5 female rats, when a single intravenous dose of 10, 30 and 100 mg/kg was given, there were no toxicities identified in any of the study endpoints of mortality, clinical signs, body weights, food consumption, ophthalmological examination, haematology, blood chemistry, urinalysis and post-mortem evaluations of organ weights and macroscopic and microscopic pathology. Rats were followed for 17 days after dosing. In toxicokinetic evaluations, the exposure increased in proportion with dose and was slightly

more in males than in females: in the latter, at 100 mg/kg, AUC0-348Hr was 188,218 microghr/ml: half-life was 9-12 days. No further general toxicity studies were done in rats.

When given to 3 male cynomolgus monkeys at doses of 5 or 50 mg/kg, once intravenously, again, this was generally well tolerated with no toxicities identified on the same outcome measures as applied to rats. Monkeys were followed for 4 weeks after dosing. In toxicokinetic evaluations, the exposure increased in proportion with the 10-fold increase in dose and at 50 mg/kg, AUC0-4wk was 226,442 microghr/ml: half-life was ~13 days.

Repeat-dose toxicity
Two repeated dose general toxicity studies were done, both in cynomolgus monkeys, one over 4 weeks (b090486) and one of 39 weeks (b100068): both were in compliance with Good Laboratory Practice.

In the 4-week study, lecanemab was given intravenously once a week (5 doses) to male and female cynomolgus monkeys (3 animals/sex/group) at 0 (vehicle), 5, 15 and 50 mg/kg. Necropsy was scheduled at 1 week, or 5 weeks (recovery groups for 0 and 50 mg/kg doses) after the last dose (study days 36 and 64).

The following parameters were evaluated: mortality, clinical signs, body weights, food consumption, urinalysis, haematology, blood chemistry, ophthalmoscopy, toxicokinetics, antibody to lecanemab, organ weights and macroscopic and microscopic pathology. Safety pharmacology endpoints (detailed clinical signs with functional observational battery, whole body plethysmography, electrocardiography, blood pressure, body temperature) were also evaluated.

No abnormalities were noted in clinical observation including those in the detailed clinical observations with functional observational battery. There was no toxicity identified on measures indicated above. However, there were increases in spleen absolute weight and/or the size and number of germinal centres seen in males at 15 and 50 mg/kg and in females at 50 mg/kg: the company considered this reflected an adaptive response to foreign (human) protein.

The no-observed-adverse-effect-level (NOAEL) dose was set as the highest used of 50 mg/kg. At this dose, the day C_{max} and AUC on day 29 were determined to be 268,000 and 189,000 microghr/ml and 2640 and 1970 microg/ml in males and females respectively. No antibodies to lecanemab were detected.

In the 39-week study (B100068), lecanemab was given intravenously once a week (40 doses) to male and female cynomolgus monkeys (4 animals/sex/group) at 0 (vehicle), 15, 50 and 100 mg/kg. These monkeys weighed 2.6-5.6 kg at the start of dosing. Necropsy was scheduled at week 39 (day 281) for all doses and also at week 52 (day 365) for monkeys dosed at 0 and 50 mg/kg (recovery groups). Two lots of lecanemab (PD09148 and PD09229) were used. Dosing was as a single dose per day at doses of 15 and 50 mg/kg groups and as two injections per day at 0 and 100 mg/kg group: this was to maximise the top dose.

The same parameters as listed above for the 4-week study were evaluated.

There was no toxicity identified in this study. As seen in the 4-week study, there was a tendency for an increase in spleen weight with an increase in germinal centre numbers in 2 of 4 females given 100 mg/kg: this was not seen in males nor in any monkeys at the end of the

recovery period. The company considered this to be a non-specific response to foreign protein; the company also considered that lecanemab might bind to amyloid beta or similar proteins in spleen and elicit a phagocytic response causing this enlargement. Detailed examination of brain slides from cerebrum (frontal, temporal and parietal lobes), diencephalons, cerebellum, midbrain, pons, and meduiia obiongata did not identify any toxicity in these measures. These evaluations were included to identify possible microhaemorrhages reported in human patients.

The company set a NOAEL dose of 100 mg/kg. Table 6 below gives the toxicokinetic data generated from this study. Overall, there was no difference between males and females and exposure increased in approximate proportion to dose; on repeated dosing, comparing between days 1 and 92, there was an increase in AUC indicating accumulation but with no difference between day 92 and 274 indicating steady state had been reached. The estimated half-life after the last dose in males and females were 419 and 410 hours, respectively. No antibodies to lecanemab were identified.

Table 6. Toxicokinetic summary

Dose (mg/kg)	Day	Male		Female	
		$C_{5min/3h5min}$ (µg/mL)	$AUC_{(0-168hr)}$ (µg•hr/mL)	$C_{5min/3h5min}$ (µg/mL)	$AUC_{(0-168hr)}$ (µg•hr/mL)
15	Day 01	421 ± 85	28100 ± 5700	340 ± 32 [a]	26900 ± 800 [a]
	Day 92	988 ± 157	106000 ± 36000	812 ± 135	92100 ± 16400
	Day 274	1170 ± 300	120000 ± 41000	937 ± 272	103000 ± 29000
50	Day 01	1520 ± 140	114000 ± 6000	1280 ± 260	96400 ± 18800
	Day 92	3680 ± 440	405000 ± 37000	2950 ± 290	361000 ± 42000
	Day 274	3310 ± 850	353000 ± 75000	2610 ± 390	293000 ± 60000
100	Day 01	2270 ± 250	173000 ± 5000 [b]	2340 ± 270	171000 ± 18000
	Day 92	5390 ± 240	584000 ± 57000	4190 ± 330	485000 ± 37000
	Day 274	4150 ± 280	463000 ± 40000	4760 ± 950	574000 ± 72000

The values are the mean ± SD from 4 or 6 animals.
$C_{5min/3h5min}$: C_{5min} for 15 and 50 mg/kg groups and C_{3h5min} for 100 mg/kg group
a: The values are the mean ± SD from 3 animals, since the concentrations from 1 female (Animal No. 50203) were excluded from calculation.
b: The values are the mean ± SD from 5 animals, since AUC from 1 male (Animal No. 10401) was excluded from calculation.

Study W-2010-0318

A further safety study was performed to evaluate effects of the murine anti-amyloid beta antibody, mab158, in Tg2576 mice. This study was not intended to be in compliance with Good Laboratory Practice. The primary focus of this study was to evaluate potential for microhaemorrhages in plaque-bearing mice given treatment with mAb158.

mAb158 was given by intraperitoneal injection at doses of 0, 1, 5, 15 and 50 mg/kg once weekly to groups of 17 or 18 female Tg2576 mice. These mice were aged 53 weeks old at the study start and dosing continued for 4 months (18 doses). Five days after the last dose, mice were killed and brains removed and prepared for storage and later evaluation. Mice were subject to macroscopic examination at necropsy and tissues prepared for microscopic examination of brains and major organs and tissues.

In a subset of each dose group, blood was collected by the tail vein at 2, 8, 24, 96 and 168 hours after the 1st and 17th doses and also immediately before the 3rd, 5th, 7th, 9th, 11th, 13th, 15th and 18th doses: plasma mAb158 and antibody to mAb158 were determined by ELISA and surface plasmon resonance (SPR) biosensor, respectively.

After homogenisation and further sample preparation steps, brain tissue concentrations of each of amyloid beta (Aβ) protofibrils, Aβ(x-40), Aβ(x-42), Aβ(1-40), and Aβ(1-42) were measured by ELISA.

Brain sections were also prepared for immunostaining with antibody to amyloid beta 42 and antibody to amyloid beta 40 or stained with Thioflavin S. Other brain sections and other organs were stained with Hematoxylin and eosin or Berlin blue for microscopic examination for microhaemorrhage and haemosiderin.

There were 6 unscheduled deaths in this study: 3 were in the control group and 1 was from each of the dose groups 5, 15 and 50 mg/kg. The company attributed these deaths to intrinsic mortality of Tg2576 mice of this age.

Table 7, below, shows concentrations of brain soluble amyloid beta protofibrils, amyloid beta (x-42), amyloid beta (x-40), amyloid beta (1-42) and amyloid beta (1-40) as measured by ELISA. At 50 mg/kg, there were reductions in amyloid beta protofibrils and amyloid beta (1-42) of 25.5 and 33.3%, respectively, compared to controls. At 5 mg/kg there was an increase of 80.8% in concentrations of amyloid beta (x-40).

Table 7. Effects of mAb158 on (Aβ) protofibrils, Aβ(x-42), Aβ(x-40), Aβ(1-42), and Aβ(1-40) in soluble fractions of Tg2576 mouse brains

Treatments	Brain PF (Aβ42 pmol/L)	Soluble Aβ(x-42) (ng/g brain)	Soluble Aβ(x-40) (ng/g brain)	Soluble Aβ(1-42) (ng/g brain)	Soluble Aβ(1-40) (ng/g brain)
PBS	4593 ± 931	13.1 ± 3.2	50.5 ± 6	4.5 ± 0.8	23.6 ± 2.9
mAb158 1 mg/kg	4481 ± 803	11.8 ± 2.8	69.6 ± 7.7	4.9 ± 0.8	35.1 ± 3.7
mAb158 5 mg/kg	5467 ± 1055	20.1 ± 3.9	91.3 ± 10.0*	6.1 ± 1.1	32.4 ± 3.7
mAb158 15 mg/kg	3528 ± 714	15.1 ± 3.4	69.9 ± 6.2	4.3 ± 0.9	24.0 ± 3.9
mAb158 50 mg/kg	1170 ± 309*	5.4 ± 1.3	62.8 ± 5.6	1.5 ± 0.3*	23.1 ± 2.8

Female Tg2576 mice aged 53 weeks were administered mAb158 intraperitoneally at 1, 5, 15, and 50 mg/kg/week for 4 months. Brain samples were obtained 5 days after the final mAb158 treatment, and Aβ species were extracted with TBS. Aβ protofibril, Aβ(x-42), Aβ(x-40), Aβ(1-42) and Aβ(1-40) levels were measured by ELISA. Protofibril levels are reported as Aβ(1-42) pmol/L-equivalents. Data are presented as means ± SEM. Aβ = amyloid β, PBS = phosphate buffered saline, PF = protofibril, TBS = Tris-buffered saline.
* $P < 0.05$ indicates significant difference from PBS control group (Dunnett's test).

Table 8 shows concentrations of brain insoluble amyloid beta (x-42), amyloid beta (x-40), amyloid beta (1-42) and amyloid beta (1-40) as measured by ELISA. Concentrations of insoluble Aβ(x-40) and Aβ(1-40) increased in mice given 5 mg/kg mAb158, compared with controls. There was no other significant change.

The mean brain protofibril level in soluble fractions from mice rated as antibody negative / equivocal was ~10% that of controls. The mean brain Aβ(1-42) and Aβ(x-42) levels in soluble fractions from mice rated as antibody negative / equivocal were ~18 and 23% that of controls, respectively.

Table 8. Effects of mAb158 on Aβ(x-42), Aβ(x-40), Aβ(1-42), and Aβ(1-40) in insoluble fractions of Tg2576 mouse brains

Treatments	Insoluble Aβ(x-42) (µg/g brain)	Insoluble Aβ(x-40) (µg/g brain)	Insoluble Aβ(1-42) (µg/g brain)	Insoluble Aβ(1-40) (µg/g brain)
PBS	6.6 ± 0.6	15.8 ± 1.9	4.5 ± 0.5	15.8 ± 1.9
mAb158 1 mg/kg	7.9 ± 0.5	19.3 ± 2.1	5.3 ± 0.4	18.3 ± 2.0
mAb158 5 mg/kg	7.5 ± 0.6	25.4 ± 2.2*	5.5 ± 0.4	22.8 ± 1.9*
mAb158 15 mg/kg	6.1 ± 0.6	19.6 ± 2.6	4.1 ± 0.4	16.9 ± 2.2
mAb158 50 mg/kg	5.9 ± 0.5	20.9 ± 1.9	3.7 ± 0.3	15.7 ± 1.6

Female Tg2576 mice aged 53 weeks were administered mAb158 intraperitoneally at 1, 5, 15, and 50 mg/kg/week for 4 months. Brain samples were obtained 5 days after the final mAb158 treatment, and Aβ species were extracted with 70% FA, following an extraction with TBS. Brain Aβ(x-42), Aβ(x-40), Aβ(1-42), and Aβ(1-40) levels were measured by ELISAs. Data are presented as means ± SEM. Aβ = amyloid β, FA = formic acid, PBS = phosphate buffered saline, TBS = Tris-buffered saline. * $P < 0.05$ indicates significant difference from PBS control group (Dunnett's test).

In measurements of brain plaques, there was no significant change in mice given any dose of mAb158 (Tables 9 and 10).

Table 9. Effects of mAb158 on 6E10- and thioflavin S-positive plaques in Tg2576 mouse brains.

Treatments	6E10-positive plaques Cortex (%)	6E10-positive plaques Hippocampus (%)	Thioflavin S-positive plaques Cortex (%)	Thioflavin S-positive plaques Hippocampus (%)
PBS	0.66 ± 0.07	0.36 ± 0.07	0.33 ± 0.05	0.17 ± 0.05
mAb158 1 mg/kg	0.63 ± 0.10	0.35 ± 0.05	0.29 ± 0.06	0.19 ± 0.04
mAb158 5 mg/kg	0.61 ± 0.09	0.39 ± 0.11	0.29 ± 0.04	0.18 ± 0.06
mAb158 15 mg/kg	0.55 ± 0.08	0.29 ± 0.07	0.28 ± 0.05	0.11 ± 0.02
mAb158 50 mg/kg	0.38 ± 0.06	0.21 ± 0.05	0.19 ± 0.04	0.11 ± 0.02

6E10- and Thioflavin S-positive plaques were measured by using Axiovision image-analyzing software. Data indicate % of Aβ plaque area in the total area of the indicated brain region. Data are presented as means ± SEM. PBS = phosphate buffered saline.

Table 10. Effects of mAb158 on plaques immunostained with anti-Aβ42 and anti-Aβ40 antibodies in Tg2576 mouse brains

Treatments	Aβ42-positive plaques Cortex (%)	Aβ42-positive plaques Hippocampus (%)	Aβ40-positive plaques Cortex (%)	Aβ40-positive plaques Hippocampus (%)
PBS	0.27 ± 0.03	0.13 ± 0.03	0.41 ± 0.07	0.19 ± 0.05
mAb158 1 mg/kg	0.25 ± 0.04	0.16 ± 0.03	0.37 ± 0.08	0.26 ± 0.06
mAb158 5 mg/kg	0.26 ± 0.04	0.20 ± 0.06	0.40 ± 0.06	0.27 ± 0.12
mAb158 15 mg/kg	0.24 ± 0.03	0.11 ± 0.02	0.39 ± 0.06	0.14 ± 0.03
mAb158 50 mg/kg	0.22 ± 0.04	0.09 ± 0.02	0.24 ± 0.05	0.12 ± 0.03

Aβ42- and Aβ40-positive plaques were measured by using Axiovision image-analyzing software. Data indicate % of Aβ plaque area in the total area of the indicated brain region. Data are presented as means ± SEM. PBS = phosphate buffered saline.

In the histopathological analyses, the report stated there were no mAb158-related changes in any organs and tissues examined. Microhaemorrhage, inflammatory changes or microglial activation were not detected.

Focal mononuclear infiltrations with occasional neutrophils were observed in the meninges and choroid plexus in some mice irrespective of treatment: this was judged by the company as not related to mAb158.

In kinetic evaluations, Cmax and AUC0-168h for mAb158 increased in a dose-proportional manner after the 1st injection. The AUC0-168h ratios of the 17th to the 1st dose were in the range of 0.03 to 0.53 indicating an immunogenic response to reduce exposure to mAb158. After the 18th dose, there were the following numbers in each group that were rated as positive for antibody to mAB158: 15/17, 16/16, 13/16 and 10/16 mice at 1, 5, 15 and 50-mg/kg. Trough mAb158 concentrations prior to the 18th dose were ~100-fold higher in mice that did not show an antibody response as compared to those that did.

Interspecies comparison

The company presented table 11 below to support the apparent safety margins. Using values for human steady state AUC0-t of 37,700 microgh/ml and Cmax of 307 µg/ml at 10 mg/kg every 2 weeks (derived from study No. BAN2401-A001-101), the safety studies in rats and monkeys provided apparent margins of 5 – 27-fold. The study in mice used a different antibody and so quantitative comparisons do not seem to be meaningful. Based on this comparison, doses used in general toxicity studies in rats and monkeys are considered to be sufficient to ensure excess exposure compared to that intended in human patients.

Table 11. Safety margins to clinical dose

Study	mAb	Endpoint	Dose (mg/kg)	AUC (µg·h/mL)	AUC Safety Margin[a]	C_{max} (µg/mL)	C_{max} Safety Margin[a]
Single-dose rat	lecanemab	NOAEL	100	202,525[b]	5	2358[c]	8
39-week monkey	lecanemab	NOAEL	100	518,500[d]	27	4455[e]	14
18-week Tg2576 mice	mAb158[f]	NOAEL	50	40,439[g]	2	356[h]	1

AUC(0-τ) = AUC over the dosing interval on multiple dosing, AUC(0-x) = AUC from zero time to fixed timepoint x, C5min, = concentration at 5 minutes, C3h5min, = concentration at 3 hours and 5 minutes a: Based on a human steady state AUC0-t of 37,700 µg·h/mL and Cmax of 307 µg/mL at the clinical dose of 10 mg/kg every 2 weeks. b: Mean AUC(0-384h) for males and females. c: Mean C5min for males and females after dosing. d: Mean AUC(0-168h) for males and females. Exposure value was multiplied by 2 in margin calculation to account for an AUC which is equal to the dosing interval in humans. e: Mean C3h5min for males and females on Day 274. f: Surrogate murine antibody of lecanemab g: Mean AUC(0-168h) following 17th administration. Exposure value was multiplied by 2 in margin calculation to account for an AUC which is equal to the dosing interval in humans. h: Mean Cmax following 17th administration.

Genotoxicity

No genotoxicity studies were performed. It is not expected that lecanemab can interact directly with deoxyribonucleic acid (DNA) or other chromosomal material.

Carcinogenicity

No carcinogenicity studies were performed. Rodent carcinogenicity studies are not relevant for this product.

Reproductive and developmental toxicity

No reproductive, developmental or juvenile animal toxicity studies were performed. These were considered as not necessary to support use in the intended target patient population due to age, likely to be 50 and over. In the 39-week general toxicity study in monkeys there were no concerns raised about potential toxicity of lecanemab to male or female reproductive organs.

Local tolerance

A separate local tolerance study was performed in monkeys dosed by subcutaneous injection over 4 weeks (report b200192). This study was in compliance with Good Laboratory Practice.

Lecanemab was given by subcutaneous injection once daily for 28 days to 4 male and 4 female cynomolgus monkeys at 10 mg/kg (concentration: 200 mg/ml). A control group (4 monkeys/group/sex) were given the same volume (0.05 ml/kg) of vehicle of 25 mM histidine, 200 mM arginine and 0.05% Polysorbate 80). The dosing site was rotated through 4 different areas and necropsy was scheduled for 3 days after the last dose.

Assessment of toxicity was based on mortality, clinical signs, including observation of the injection sites, body weights, food consumption, haematology, blood chemistry, toxicokinetics, anti-drug antibody (ADA) analysis, macroscopic examination, and microscopic examination of the injection sites, axillary lymph node, inguinal lymph node, and spleen.

There were no deaths, and no toxicity was identified at the injection sites or in other measures. Toxicokinetic data are given in the table below: no antibodies to lecanemab were detected. Lecanemab was judged to be well tolerated by subcutaneous injection at 200 mg/ml.

Table 12. Toxicokinetic summary

Dose (mg/kg)	Day	Male			
		C_{max} (µg/mL)	t_{max} (hour)	$AUC_{(0-24h)}$ (µg·h/mL)	$AUC_{(0-72h)}$ (µg·h/mL)
10	1	52.4 ± 11.6	24.0 ± 0.0	657 ± 145	NA
	28	1470 ± 110	1.50 ± 1.73	32,000 ± 1300	92,900 ± 3500

Dose (mg/kg)	Day	Female			
		C_{max} (µg/mL)	t_{max} (hour)	$AUC_{(0-24h)}$ (µg·h/mL)	$AUC_{(0-72h)}$ (µg·h/mL)
10	1	54.6 ± 15.1	20.0 ± 8.0	797 ± 366	NA
	28	1610 ± 170	5.00 ± 3.83	32,600 ± 4000	90,100 ± 9300

Data represent the mean ± SD of 4 animals.
$AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to 24 hours,
$AUC_{(0-72h)}$ = area under the concentration-time curve from zero time to 72 hours,
C_{max} = maximum observed concentration, t_{max} = time at which the highest drug concentration occurs.
NA: not applicable.

Other toxicity studies

Specific studies into haematocompatibility, potential for cytokine release, antigenicity, immunotoxicity, dependence, metabolites and impurities were not performed.

Conclusion on toxicology

Lecanemab is an IgG1 monoclonal antibody that binds to amyloid beta. The cross-reactivity studies showed that lecanemab did bind to brain tissue from patients with Alzheimer's disease as expected. There was binding to central nervous system tissues of cynomolgus monkeys but not to any tissues from rats. In general toxicity studies in monkeys with dosing for up to 39 weeks with 13 weeks post-dose follow-up, there was no toxicity identified and the highest doses used were considered to be the NOAEL doses. This was also the case when the drug was given repeatedly over 4 weeks subcutaneously to cynomolgus monkeys.

Safety pharmacology assessments for lecanemab were conducted as part of repeat-dose general toxicity studies in cynomolgus monkeys. Lecanemab did not notably affect cardiovascular, respiratory, or central nervous systems at doses up to 100 mg/kg.

No antibodies to lecanemab were identified in testing in cynomolgus monkeys either by subcutaneous or intravenous dosing. There was no loss in exposure on repeated dosing of lecanemab; on repeated dosing, there was clear evidence of accumulation when given once weekly.

The doses used in monkeys are judged adequate to ensure that exposure was higher in monkeys than is anticipated in human patients given the recommended dose. Once weekly dosing resulted in exposure in monkeys that was 27-fold and 14-fold (for AUC and for Cmax respectively) exposure in humans.

No microhaemorrhage and haemosiderin deposition was seen in a study in older Tg2576 mice given the murine antibody mAb158; mAb158 produced a notable decrease in amyloid beta concentrations in the brain. There were also no inflammatory changes or microglial activation seen.

The fact that there were no cerebral microhaemorrhages in transgenic mice given mAb158 is encouraging but it is at variance with what is reported in the literature for some other antibodies that target amyloid beta. The company hypothesise that the reason why brain microhaemorrhages did not increase in the transgenic mouse studies with mAb158 may be due to mAb158's high avidity to Aβ protofibrils. Lecanemab bound to the fibrils with an avidity that was 1.4- to 11-fold lower than the avidity for the protofibrils, and to monomers and oligomers with lower avidities than the avidity for the fibrils. The targets of other anti-Aβ antibodies that demonstrated an increase in brain microhaemorrhages include not only Aβ protofibrils, the main target of lecanemab, but also other Aβ conformations such as monomers, oligomers, and fibrils. The explanation that different antibodies have a different profile of action against different forms of amyloid is adequate.

As described in the pharmacology section above, the potential for off-target binding was explored by identification of lecanemab-interacting proteins in the plasma from rat, mouse, cynomolgus monkey, healthy human subjects, and AD subjects as detected by immunoprecipitation followed by western blot analysis. A 150 kDa band was immunoprecipitated from all samples analysed, and the 150 kDa band from human plasma was identified as thrombospondin-1 (THBS1) by mass spectrometry. The amino acid sequence homology of THBS1 between human and cynomolgus monkey or human and murine is known to be high (99.23% or 94.70%, respectively), and lecanemab is likely to bind to monkey or murine plasma THBS1.

The data implies the possibility that lecanemab did bind thrombospondin-1 in monkeys and did not cause bleeding. As the monkeys were healthy, the studies in monkeys do not take account of a possible interaction between disease pathology and thrombospondin-1 interactions. The explanation for why some people, very notably a minority, develop bleeding on treatment with lecanemab should be sought from studies in humans.

The absence of reproductive toxicity testing is acceptable for this indication. The product is likely to be used in patients who are over 50 years of age. The SmPC does include warnings for use requiring contraception if used in female patients considered to be of child-bearing potential. The absence of amyloid beta in animals of fertile age makes the conduct of a study in pregnant animals of limited value.

The absence of genotoxicity and of carcinogenicity studies are each acceptable. As a monoclonal antibody, there is no expectation that lecanemab would interact with the genome as it does not enter cells. A rodent carcinogenicity study is not applicable for this product. General toxicity studies with dosing over 39 weeks and exposure over ~1 year did not show tissue hyperplasia or compromise to the immune system in monkeys.

Dependence is not considered a risk with lecanemab: in the studies completed, there were no findings to indicate withdrawal symptoms and there is no pharmacological rationale for a risk of dependence.

The environmental risk posed by the product is judged to be minimal given the active ingredient is likely to be broken down in the body to its constituent amino acids and there are no novel excipients.

Overall, these safety studies are an appropriate set of data to characterise the exposure to and effect of lecanemab. The lack of toxicity in these studies is sufficient to conclude that no further toxicity studies are needed in animals.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). In line with current regulatory guidance applicable to proteins (CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/000 corr 2)) experimental studies supporting an ERA are not required. As lecanemab is a humanised monoclonal antibody and contains no novel excipients (these being arginine, histidine and polysorbate 80), this stance is agreed.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application:

- Phase 1 studies that evaluated single or multiple doses of lecanemab, (0.1 to 15 mg/kg) administered to subjects with mild to moderate Alzheimer's disease (AD) (BAN2401 A001 101) and mild cognitive impairment (MCI) due to AD and mild AD (BAN2401 J081 104).
- One dose-range finding, Phase 2 study and one pivotal Phase 3 study in subjects with early AD (EAD): Study 201 is a Phase 2 study with a Core and an Open-label Extension (OLE) Phase and Study 301 is a Phase 3 study with a Core and an OLE Phase. Study 301 Core and Study 201 Core have completed; the 301 OLE Phase and 201 OLE Phase are ongoing.

In addition, as part of the clinical development plan for lecanemab, a Phase 3 study (BAN2401-G000-303) in subjects with preclinical AD, and a Phase 2/3 study (DIAN-TU-001) in subjects with Dominantly Inherited Alzheimer's Disease (DIAD) are also ongoing. In DIAN-TU-001 subjects will receive open-label lecanemab as background treatment, however no subjects had been dosed by the data cutoff for this submission.

All studies were conducted in line with current Good Clinical Practice (GCP).

Bioanalytical methods

The bioanalytical methods employed for lecanemab clinical studies included methods to determine the serum and CSF concentrations of lecanemab for pharmacokinetic (PK) parameter assessment, and the presence of anti-drug antibody (ADA) and neutralizing anti-drug (lecanemab) antibodies (NAb). These methods were validated per current regulatory requirements.

The biomarker (fluid [plasma and CSF]) and apolipoprotein E4 (ApoE4) genotyping methods used in the clinical studies were either from commercially available kits that demonstrated adequate sensitivity and reproducibility or conducted under Clinical Laboratory Improvement Amendments (CLIA).

Detection of ADA was performed using a tiered approach involving screening, confirmatory, and titer assays.

The current bioanalytical method for ADAs has a limited drug tolerance level of 31.3 µg/mL

for lecanemab. The applicant has advised that a more sensitive ADA assay with an increased drug tolerance is currently in development. The applicant is proposing to submit a reanalysis of the samples from study 301 core in late 2025. Provision of this new data, together with a re-evaluation of any impact of immunogenicity on efficacy, safety and PK is a post-authorisation commitment.

IV. 2 Pharmacokinetics

In clinical studies, lecanemab was supplied as a liquid drug product in vials and diluted with saline before administration via the intravenous route. The intended commercial product will be administered by intravenous infusion. There were 3 formulations used in clinical development:

- Process A1/Formulation A1 in Phase 1/2 studies
- Process B1/Formulation B1 in Phase 2/3 studies
- Process C/Commercial Formulation A1 in Phase 3 studies

Summary of completed pharmacokinetic (PK) studies

Study 101

This was a randomised, double-blind, placebo-controlled, combined single ascending dose (SAD) and multiple ascending dose (MAD) study to assess safety, tolerability, immunogenicity, pharmacodynamic response, and pharmacokinetics of intravenous infusions of BAN2401 in subjects with mild to moderate AD.

Objectives:
In the SAD part, the primary objectives were to evaluate safety and tolerability of single intravenous infusions of lecanemab at sequentially ascending doses; to assess the PK of lecanemab in serum and cerebrospinal fluid (CSF); and to assess the immunogenicity (production of serum anti lecanemab antibody) of lecanemab after single intravenous infusion.

In the MAD part, the primary objectives were to evaluate the safety and tolerability of 4 monthly intravenous infusions of lecanemab at sequentially ascending doses; to evaluate the safety and tolerability of 7 biweekly intravenous infusions of lecanemab at the highest dose; to assess the PK of lecanemab in serum and CSF; and to assess the immunogenicity (production of serum anti-lecanemab antibody) of lecanemab.

Study Design and Methodology:
The study was composed of 2 parts, SAD and MAD. Randomisation in both the SAD and MAD parts occurred after subjects underwent non-contrast brain magnetic resonance imaging (MRI) during the Screening Period. In the SAD, 48 eligible adult subjects with mild to moderate AD were randomised (3:1), respectively, to receive either lecanemab or placebo administered as a single 60- to 75-minute intravenous infusion. Treatment consisted of sequential, MAD in 6 cohorts (0.1, 0.3, 1.0, 3.0, 10.0, and 15.0 mg/kg). Twelve subjects received placebo.

In the MAD, 24 subjects received sequential SAD (one dose per 4 weeks; total of 4 doses for 0.3 mg/kg, 1 mg/kg, and 3 mg/kg and one dose per 2 weeks; total of 7 doses for 10 mg/kg) in 4 cohorts of 8 subjects (6 active and 2 placebo). Eight subjects received placebo.

Results:

SAD Serum Lecanemab Concentrations

Mean (SD) PK parameters for SAD cohorts 1 through 6 on Day 1 are summarised in Table 1. The mean Cmax and the mean area under the concentration versus time curve from 0 to 24 hours (AUC(0-24h)) increased in approximate proportion to increasing doses of lecanemab.

After intravenous infusion of a single dose of lecanemab over approximately a 1-hour interval, the median time at which the highest drug concentration occurred at 1.78 to 2.20 hours from the start of infusion (Table 1). Single doses of lecanemab over 0.3 to 15 mg/kg showed 1st order elimination kinetics. Because of the limited number of post dose time points at which lecanemab concentrations were measurable, the mean t½ of lecanemab could be estimated only for subjects who received higher doses. The mean t½values for the 3 mg/kg, 10 mg/kg, and 15 mg/kg doses were, respectively, 83.5 hours (3.5 days), 165 hours (6.9 days), and 174 hours (7.3 days). The slightly longer t½observed at the higher doses is considered likely due to the extended characterization of concentration-time profiles.

Figure 1: Mean Serum Concentration-Time Profile of Lecanemab - Study 101 (PK Analysis Set)

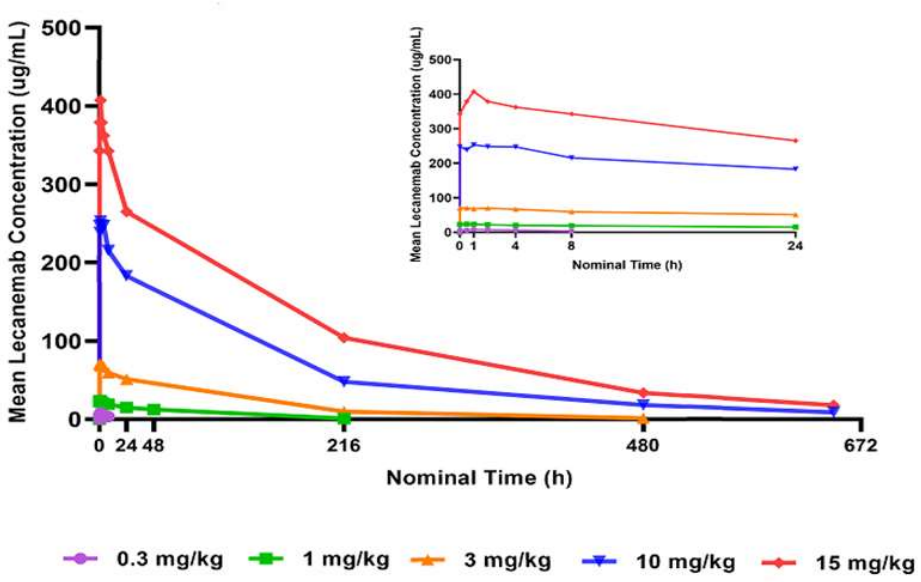


Table 1: Pharmacokinetic Parameters of Lecanemab after Single Intravenous Administration in Study 101 (PK Analysis Set)

Cohort [a,b]	Dose (mg/kg)	C_{max} (µg/mL)		t_{max} (hours)	$AUC_{(0-24h)}$ (µg*h/mL)		$AUC_{(0-t)}$ (µg*h/mL)		$AUC_{(0-inf)}$ (µg*h/mL)		$t_{1/2}$ (hours)
		Mean (SD)	CV%	Median (min, max)	Mean (SD)	CV %	Mean (SD)	CV %	Mean (SD)	CV %	Mean (SD)
SAD2	0.3	8.50 (2.42)	25.3	2.20 (1.50, 5.00)	136[c]	NC[c]	43.8 (21.1)	60.3	NC	NC	NC
SAD3	1	24.7 (3.62)	14.7	1.78 (1.28, 5.00)	432 (99.6)	22.2	1090 (959)	67.8	NC	NC	103[d] (-)
SAD4	3	74.2 (11.1)	14.8	1.83 (1.22, 5.20)	1390 (140)	9.75	7170 (1320)	20.6	7430 (1210)	17.7	83.5 (13.7)
SAD5	10	264 (32.4)	12.4	2.00 (1.23, 5.13)	5010 (550)	11.0	35,700 (6070)	19.2	38,000 (7340)	22.0	165 (45.5)
SAD6	15	418 (54.5)	13.1	2.00 (2.00, 3.00)	7630 (593)	8.06	62,000 (14700)	26.2	66,900 (17600)	29.8	174 (36.1)

$AUC_{(0-24h)}$ = area under the concentration-time curve from zero time to fixed time-point 24 h, $AUC_{(0-t)}$ = area under the concentration-time curve from zero time to time of last quantifiable concentration, $AUC_{(0-inf)}$ = area under the concentration-time curve from zero time extrapolated to infinite time, CV% = coefficient of variance, IV = intravenous, min = minimum, max = maximum, NC = not calculated due to insufficient data, PK = pharmacokinetic, SAD = single ascending dose, $t_{½}$ = terminal elimination phase half- life, t_{max} = time at which the highest drug concentration occurs.

MAD Serum Lecanemab Concentrations

When lecanemab was administered monthly for up to 4 doses in the dose range of 0.3 to 3 mg/kg (MAD1 to MAD3) and biweekly for up to 7 doses at the dose level of 10 mg/kg (MAD4), the median time to maximum concentration at the first dose was 1.67 to 2.08 hours after the start of infusion, similar to that at the final dose (1.61 to 2.32 hours). The mean Cmax and AUC(0 24h) values of lecanemab increased approximately proportionally with lecanemab dose across the range of 0.3 to 10 mg/kg after the first and final (4th or 7th) infusions. The PK profile during the elimination phase was consistent with first-order kinetics. The mean t½ of lecanemab ranged from 105 to 133 hours (4.4 to 5.5 days) (Table 2). There was no apparent accumulation of lecanemab in serum after 4 successive doses administered monthly in the range of 0.3 to 3 mg/kg.

In the MAD4 cohort (Lecanemab 10 mg/kg biweekly; LEC10-BW), steady state was achieved after the 3rd of 7 doses (i.e., after approximately 6 weeks of treatment). The minimum observed concentration at steady state (Css,min) was 40 µg/mL. The calculated accumulation ratio (Rac) based on AUC was 1.39.

Table 2: Lecanemab PK Parameters after the 1st and Last Intravenous Administration in Study 101 (PK Analysis Set)

Cohort (Dose Level, mg/kg)[a]	Dose Day	In-fusion No.	C_{max} (µg/mL)		t_{max} (hours)	$AUC_{(0\text{-}24h)}$ (µg·h/mL)		$AUC_{(0\text{-}t)}$ (µg·h/mL)		$t_{½}$ (hours)
			Mean (SD)	CV%	Median (min, max)	Mean (SD)	Mean (SD)	Mean (SD)	CV%	
MAD1 (0.3) Monthly	1	1	7.62 (0.63)[b]	8.44	1.75 (1.00, 2.02)[b]	156 (12.1)[c]	7.73	NA[d]	NA[d]	NC
	84	4	7.26 (1.53)	20.7	2.32 (1.03, 5.42)	133 (23.4)	17.0	NA[d]	NA[d]	NC
MAD2 (1.0) Monthly	1	1	30.9 (3.54)	12.0	2.00 (1.00, 3.22)	548 (68.9)	12.7	NA[d]	NA[d]	133 (20.6)
	84	4	30.6 (4.59)[e]	15.6	1.61 (1.17, 5.07)[e]	470 (110)[c]	25.1	NA[d]	NA[d]	NC
MAD3 (3.0) Monthly	1	1	81.4 (16.2)	20.1	2.08 (1.00, 5.53)	1380 (339)	25.1	NA[d]	NA[d]	133 (27.4)
	84	4	68.8 (8.98)[b]	13.9	2.10 (1.67, 2.42)[b]	1220 (132)[b]	11.3	NA[d]	NA[d]	NC
MAD4 (10) Biweekly	1	1	267 (61.8)	21.1	1.67 (1.27, 3.08)	4750 (1210)	23.9	27,200 (8820)	30.5	105 (22.1)
	84	7	307 (70.2)	21.5	1.88 (1.13, 3.10)	5720 (1230)	19.6	37,700 (9110)	25.5	127 (29.9)

Values are the mean (SD) except for t_{max}, which is median (min, max).$AUC_{(0\text{-}24h)}$ = area under the concentration-time curve from zero (predose) to fixed time-point 24 h, $AUC_{(0\text{-}t)}$ = area under the concentration-time curve form zero time to time of last quantifiable time concentration, CV% = coefficient of variance, MAD = multiple ascending dose, min = minimum, max = maximum, NA = not applicable, NC = mean of the PK parameter not calculated due to insufficient data, PK = pharmacokinetic,

CSF Concentrations

The CSF:serum ratio (%) at 24 hours after a single dose of lecanemab (15 mg/kg), or after the 4th dose of lecanemab given monthly at dose levels of 0.3, 1, and 3 mg/kg was within the range of 0.040 to 0.076%. Following dosing of LEC10-BW for 7 doses, the CSF: serum ratio (%) at 24 hours postdose or 14 days after the 7th dose was in the range of 0.13% to 0.29% (Table 3).

Table 3. CSF Concentrations and CSF: Serum Ratios in SAD6, MAD1, MAD2, MAD3, and MAD4 Subject Cohorts in Study 101 (PK Analysis Set)

Cohort (Dose Level, mg/kg)	Day 2[a] or Day 85[b] 24 Hours After Final Dose Mean (SD)		Day 10[a] or Day 98[c] 10[a] or 14[c] Days Postdose of Final Dose Mean (SD)	
	CSF (ng/mL)	CSF: Serum Ratio (%)	CSF (ng/mL)	CSF: Serum Ratio (%)
SAD6 (15 mg/kg) (N = 6)	96.3 (45.1)	0.043 (0.032)	72.2, 624[d]	0.07, 0.81[d]
MAD1 (0.3 mg/kg Monthly) (N = 6)	3.47 (2.13)	0.076 (0.045)	CSF not collected	
MAD2 (1 mg/kg Monthly) (N = 6)	8.89 (5.31)	0.040 (0.027)		
MAD3 (3 mg/kg Monthly) (N = 6)	25.0 (13.3)	0.058 (0.038)		
MAD (10 mg/kg Biweekly) (N = 6)	263 (106)	0.133 (0.032)	116 (109)	0.290 (0.140)

CSF = cerebrospinal fluid, MAD = multiple ascending dose, PK = pharmacokinetic, SAD = single ascending dose.

a: SAD6: CSF was collected on Day 2 (24 hours postdose) and Day 10 postdose.
b: MAD1-4: CSF was collected on Day 85 (24 hours postdose of final dose).
c: MAD4: CSF was collected on Day 98 (14 days postdose of final dose, which was Dose 7).
d: Only 2 subjects treated with lecanemab at 15 mg/kg had CSF sampling on Day 10 instead of the expected 3 subjects because 1 of these subjects had CSF sampled on Day 2 in error instead of Day 10. Of the 2 subjects with CSF concentrations on Day 10, 1 was found to have CSF concentration of 624 ng/mL (CSF: serum ratio approximately 0.81%), which was an outlier compared to the CSF: serum ratio of all other subjects who had CSF sampling for lecanemab concentration. Thus, for Day 10 CSF concentration, the mean is not provided, and individual PK data are shown for only the 2 subjects.

Key Conclusions:

- Serum lecanemab Cmax and AUC increased in approximate proportion to increasing doses.
- The mean t½ of lecanemab was 5 to 7 days when given at 1 mg/kg or higher doses.
- Consistent with the reported t½, little or no accumulation in exposure was evident after multiple monthly doses of 0.3, 1.0, and 3.0 mg/kg. At the dose level of LEC10-biweekly, steady state was achieved after 3 doses. The minimum steady state concentration achieved with LEC10-BW was 40 µg/mL, with accumulation of 1.39.
- The CSF:serum ratio (%) at 24 hours after a single dose of lecanemab (15 mg/kg), or after the 4th dose of lecanemab given monthly at dose levels of 0.3, 1, and 3 mg/kg was within the range of 0.040% to 0.076%. LEC10-BW for 7 doses, the CSF: serum ratio (%) at 24 hours or 14 days after the 7th dose was in the range of 0.13% to 0.29%.
- Lecanemab was well tolerated at doses of up to LEC10-BW for 14 weeks.

Study 104

This was a randomised, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, immunogenicity, and pharmacodynamic response of repeated intravenous infusions of BAN2401 in subjects with mild cognitive impairment due to AD and mild AD.

Objectives:

The primary objective was to evaluate the safety and tolerability of repeated intravenous infusions of lecanemab in Japanese subjects with MCI due to AD and mild AD. Secondary objectives were to evaluate the pharmacokinetics of lecanemab in serum and CSF; to

evaluate the effect of repeated intravenous infusions of lecanemab on the immunogenicity and CSF biomarkers (e.g., amyloid beta monomer from amino acid 1 to 40 Aβ[1-40], Aβ[1-42]) in Japanese subjects; and to evaluate the effect of apolipoprotein E 4 allele (ApoE4) on the safety, tolerability, and PD response of repeated intravenous infusions of lecanemab.

Study Design and Methodology:
This was a multicentre, randomised, placebo-controlled, double-blind, multiple ascending dose study in a total of 24 Japanese subjects (8 subjects per cohort: 6 for lecanemab and 2 for placebo) with MCI due to AD and mild AD. For each cohort the study consisted of a Screening Period (before randomisation), a Treatment Period (from randomisation to the last dose), and a Follow-up Period (after the last dose). Cohorts 1, 2, and 3 received doses of 2.5, 5, and 10 mg/kg of lecanemab, respectively.

In the Treatment Period, lecanemab or placebo was administered as an intravenous infusion followed by a 6-week washout period after the 1st dose. Then, lecanemab or placebo was administered once every 2 weeks over 60±10 minutes for a total of 5 infusions (8 weeks) to evaluate the safety, tolerability, and PK of lecanemab. In the 8-week Follow-up Period, safety profiles after repeated administration were evaluated.

Results:
<u>SAD Serum Lecanemab Concentrations</u>
The PK profile of lecanemab after a single intravenous infusion was linear over the dose range from 2.5 through 10 mg/kg. The time to the highest drug concentration occurred in approximately 2 hours (median), ranging from immediately after the end of infusion, 1 hour, to 4.90 hours. The mean t½, clearance (CL), and volume of distribution (volume of distribution [Vss]) were comparable across doses. The mean t½ of lecanemab after single intravenous administration at doses ranging from 2.5 through 10 mg/kg were 149 to 159 hours (6.2 to 6.6 days) (Table 4).

Figure 2: Mean Serum Concentration-Time Profile of Lecanemab after Single Intravenous Administration on Linear Scale - Study 104 (PK Analysis Set)

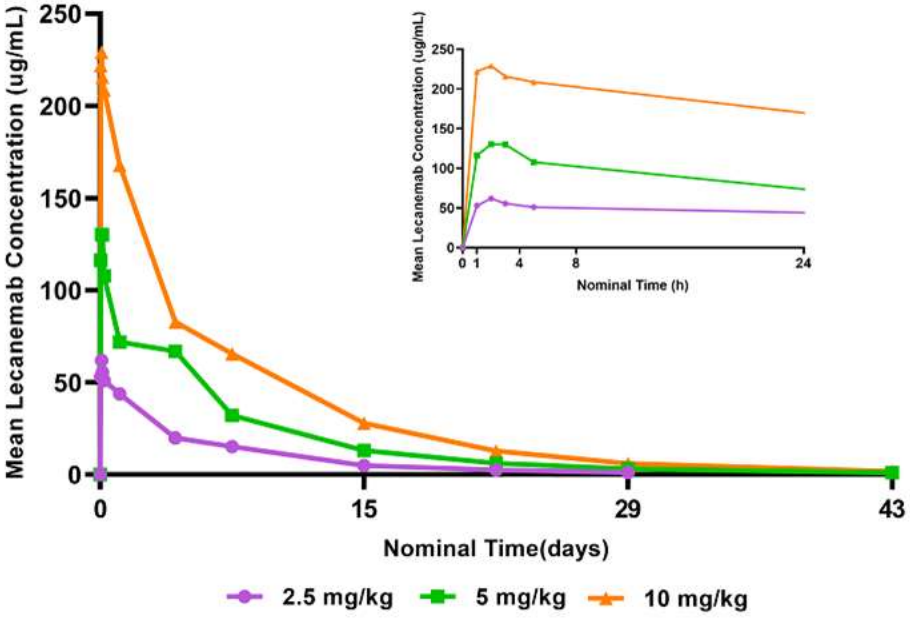


Table 4: Summary of Pharmacokinetic Parameters of Lecanemab After Single Intravenous Administration in Study 104 (PK Analysis Set)

PK Parameter	Lecanemab		
	2.5 mg/kg (N = 6)	5 mg/kg (N = 6)	10 mg/kg (N = 7)
C_{max} (µg/mL)	64.2 (13.6)	133 (9.14)	235 (34.1)
t_{max} (h)	2.140 (1.07, 4.90)	2.055 (1.95, 3.12)	2.080 (1.07, 2.87)
$AUC_{(0-t)}$ (µg•h/mL)	7070 (1180)	17,800 (6640)	32,600 (9780)
$AUC_{(0-24h)}$ (µg•h/mL)	1140 (243)	2420 (428)	4550 (639)
$AUC_{(0-336h)}$ (µg•h/mL)	6220 (1170)	14,900 (4410)	26,800 (6430)
$AUC_{(0-inf)}$ (µg•h/mL)	7320 (1120)	18,200 (6970)	33,000 (9800)
$t_{½}$ (h)	153 (30.0)	149 (52.0)	159 (16.0)
CL (L/h/kg)	0.000349 (0.0000531)	0.000310 (0.000117)	0.000325 (0.0000934)
V_{ss} (L/kg)	0.0620 (0.0155)	0.0531 (0.0137)	0.0619 (0.0122)

PK Analysis Set: (N=19).

Data are shown as mean (SD) except t_{max}, for t_{max}, median (min, max) is shown.

$AUC_{(0-24h)}$ = area under the concentration-time curve from zero (predose) to fixed time-point 24 h, $AUC_{(0-336h)}$ = area under the concentration-time curve from zero (predose) to fixed time-point 336 h, $AUC_{(0-inf)}$ = area under the concentration-time curve from zero time extrapolated to infinite time, $AUC_{(0-t)}$ = area under the concentration-time curve from zero time to time of last quantifiable concentration, CL = clearance, max = maximum, min = minimum, PK = pharmacokinetic, $t_{½}$ = terminal elimination t½, t_{max} = time at which the highest drug concentration occurs, Vass = volume of distribution at steady state.

MAD Serum Lecanemab Concentrations

Lecanemab serum concentrations increased in approximate proportion to increase in administered dose. The time at which the highest drug concentration occurs at steady state (tss,max) occurred in most subjects at 1 hour (end of infusion), or 2 hours. Steady state was achieved after the 4th of 5 doses after starting multiple dose administration once every 2 weeks. Rac, (based on Cmax) ranged from 1.12 to 1.31. Rac (based on AUC) was approximately 1.5 among all 3 dose levels (Table 5)

Table 5: Lecanemab PK Parameters after Multiple Dose Administration Once Every 2 Weeks for a Total of 5 Infusions - Study 104 (PK Analysis Set)

PK Parameter	Lecanemab		
	2.5 mg/kg (n = 6)	5 mg/kg (n = 5)[a]	10 mg/kg (n = 6)[b]
$C_{ss,max}$ (µg/mL)	72.8 (19.4)	154 (26.3)	299 (45.7)
$t_{ss,max}$ (h)	1.150 (1.03, 2.15)	1.920 (0.95, 2.83)	2.010 (1.00, 4.90)
$AUC_{(0-24h)}$ (µg•h/mL)	1380 (268)	3050 (486)	5830 (887)
$AUC_{(0-τ)}$ (µg•h/mL)	8980 (1690)	22,700 (7790)	39,500 (7330)
$R_{ac}(C_{max})$[c]	1.12 (0.0757)	1.17 (0.189)	1.31 (0.143)
$R_{ac}(AUC)$[d]	1.45 (0.136)	1.51 (0.348)	1.59 (0.220)

Data are shown as mean (SD) except $t_{ss,max}$, for $t_{ss,max}$, median (min, max) is shown.
$AUC_{(0\text{-}24h)}$ = AUC from zero (predose) to fixed time-point 24 h, $AUC_{(0\text{-}336h)}$ = AUC from zero (predose) to fixed time-point 336 h, $AUC_{(0\text{-}\tau)}$ = AUC over the dosing interval on multiple dosing, $C_{ss,max}$ = maximum concentration at steady state, max = maximum, min = minimum, PK = pharmacokinetic, $R_{ac}(AUC)$ = accumulation ratio based on AUC, defined as $AUC_{(0\text{-}\tau)}/AUC_{(0\text{-}336h)}$ after the 1st dose, $R_{ac}(C_{max})$ = accumulation ratio based on C_{max}, $t_{ss,max}$ = time at which the highest drug concentration occurs at steady state.

a: One of 6 subjects in 5 mg/kg group was excluded from noncompartmental analysis because the 6th dose was not administered.

b: One of 7 subjects in 10 mg/kg group was excluded from noncompartmental analysis because the 6th dose was not administered.

c: $R_{ac}(C_{max}) = C_{ss,max}$ (after the 6th dose)/C_{max} (after the 1st dose).

d: $R_{ac}(AUC) = AUC_{(0\text{-}\tau)}$ (after the 6th dose)/$AUC_{(0\text{-}336h)}$ (after the 1st dose).

CSF Concentrations

After 4 dose administrations once every 2 weeks, mean CSF concentrations of lecanemab ranged from 0.645% – 0.803% of serum concentrations. The CSF: serum ratios were comparable among doses ranging from 2.5 to 10 mg/kg.

Key Conclusions:

- The mean t½ of lecanemab after a single intravenous administration at doses ranging from 2.5 through 10 mg/kg were approximately 6.2 to 6.6 days.
- Serum lecanemab exposures (Cmax and AUC) after single and multiple intravenous administrations at doses ranging from 2.5 through 10 mg/kg increased in an approximately dose-proportional manner.
- Consistent with the determined t½, serum lecanemab exposures after multiple biweekly dose administration to steady state (AUC over the dosing interval on multiple dosing [AUC(0-τ)]) of doses ranging 2.5 through 10 mg/kg were approximately 50% higher than after single intravenous administration (AUC(0-336h)).
- Following multiple dose administration every 2 weeks, steady state was achieved after the 4th dose. Mean CSF concentrations of lecanemab ranged from 0.645% – 0.803% of corresponding serum concentrations.

Pharmacokinetic and PKPD models

The PK of lecanemab was analysed in blood serum at time-points as listed in studies BAN2401-A001-101, BAN2401-J081-104, BAN2401-G000-201, and BAN2401-G000-301. PK, PKPD, and Exposure-Response (ER) analyses were performed using modelling and simulation techniques.

The selection of the Population PK model was determined through a comprehensive approach. This included assessing objective function values (OFV) with a ΔOFV of 6.64 at a significance level of 0.01 and considering 1 degree of freedom (df). Additionally, the plausibility and precision of parameter estimates were taken into account, along with a graphical evaluation that included goodness-of-fit (GOF) plots. The final model was further scrutinized through Visual Predictive Checks (VPC).

To ensure robustness and reliability, nonparametric bootstrapping was carried out during the modelling process. Following model development, the final PKPD models underwent validation using nonparametric bootstrapping and were thoroughly evaluated through a prediction-corrected visual predictive check.

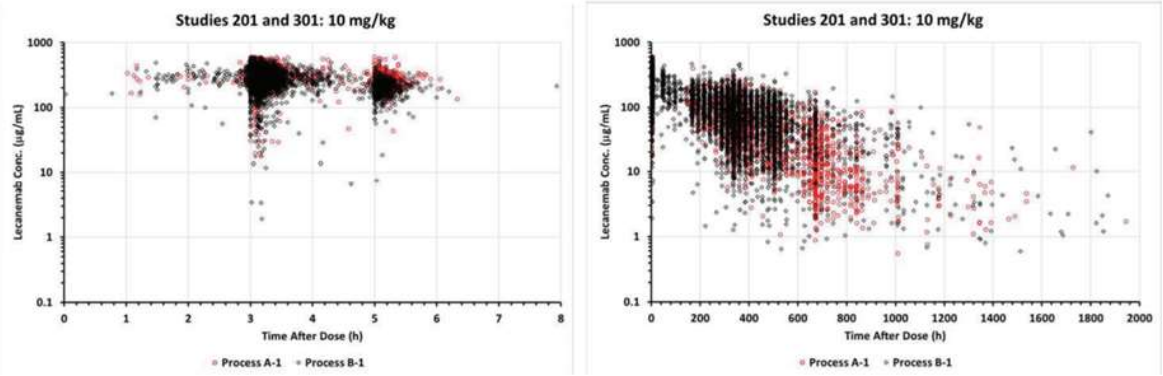
Bioequivalence

There were variations in the manufacturing procedures employed during the clinical trials compared to the commercial formulation, particularly concerning cell lines, manufacturing processes, and formulation aspects. Formulations derived from these three processes were meticulously characterised and exhibited similar physicochemical and biological attributes. Furthermore, a comparison of the pharmacokinetics of Lecanemab produced by Processes B-1 and C-1 was conducted in relation to the initial manufacturing Process A-1, as described below. Comparability has been established between formulation C2 (the to-be marketed formulation) and the other formulations through quality evaluation.

Steady state individual observed lecanemab serum concentrations versus time after dose for 10 mg/kg bi-weekly dose administered as drug product Process A-1 or drug product Process B-1 in Studies BAN2401-G000-201 and BAN2401-G000-201-301 are presented in Figure 3.

The influence of manufacturing process (Process A-1 versus Process B-1) was investigated during population PK model development. The relative bioavailability (F1) for Process B-1 was estimated at 0.904 (IIV = 8.51 %CV).

Figure 3: Observed lecanemab concentration by formulation (10 mg/kg bi-weekly) - Study BAN2401-G000-201 and BAN2401-G000-301 by process



The single 10 mg/kg IV doses of lecanemab supplied by Process A-1 and Process C-1 were administered in two separate studies, Study 101 in Cohort SAD5 and Study 004 Treatment A. As shown in Table 6 below the PK parameters of lecanemab supplied by Process A-1 and commercial Process C-1 are nearly identical supporting comparability of lecanemab exposure across manufacturing processes.

Table 6: Mean (SD) PK parameters of Lecanemab after single dose 10 mg/Kg IV, studies 101 and 004

PK Parameter	Process A-1	Process C-1
	Study 101 Cohort SAD 5	Study 004 Treatment A
N	6	30
C_{max} (µg/mL)	264 (32.4)	265 (43.3)
t_{max} (hours)	2.00 (1.23, 5.13)	2.00 (1.00, 8.00)
$AUC_{(0\text{-}inf)}$ (µg*h/mL)	38000 (7340)	37400 (9710)
$t_{1/2}$ (hours)	165 (45.5)	167 (49.1)

PK parameters are shown as mean (SD) except for t_{max}. t_{max} is presented as median (min, max).

$AUC_{(0\text{-}inf)}$ = area under the concentration-time curve from zero time extrapolated to infinite time, IV = intravenous, PK = pharmacokinetic, SAD = single ascending dose, $t_{½}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration is observed, min = minimum, max = maximum.

The to-be marketed formulation of lecanemab is different from the formulations used in clinical trials and will be produced by Process C-2. The reports demonstrating analytical similarity between the clinical and commercial formulations as per ICH Q5E guidelines are provided. These reports together with pharmacokinetic assessment of lecanemab from different processes used during clinical development provide adequate evidence to support similarity of lecanemab PK across the various manufacturing processes.

Distribution

The concentration-time profiles are characterised by a rapid distribution phase followed by a long terminal elimination phase.

Protein binding

The partitioning of lecanemab between plasma and serum was evaluated in Study EIS R1912R1. This *in vitro* study suggests differences between concentrations measured in whole blood versus serum are relatively small and within normal sample to sample variability and, consequently, it is unlikely that there is substantial binding of lecanemab to plasma proteins, such as fibrinogen, or to blood cells.

Volume of Distribution

Lecanemab PK profiles were well described by a 2-compartment model with zero order input and linear elimination from the central compartment. The population estimate of CL was low at 0.0154 L/h with an inter-individual variability of 34.9% and the population estimate of central volume of distribution was low at 3.24 L with an inter-subject variability of 12.2%.

CSF Concentrations

The CSF:serum ratio (%) at 24 hours after a single dose of lecanemab (15 mg/kg), or after the 4th dose of lecanemab given monthly at dose levels of 0.3, 1, and 3 mg/kg was within the range of 0.040 to 0.076%. Following dosing of LEC10-BW for 7 doses, the CSF:serum ratio (%) at 24 hours post dose or 14 days after the 7th dose was in the range of 0.13% to 0.29% (Study 101).

After 4 dose administrations once every 2 weeks in Study 104, mean CSF concentrations of lecanemab ranged from 0.645% – 0.803% of serum concentrations. The CSF: serum ratios were comparable among doses ranging from 2.5 to 10 mg/kg (Study 104).

CSF concentrations in Phase 1 Studies 101 and 104 demonstrated variability but fell within the range of the larger Study 301 Core dataset. Literature supports the similarity of CSF concentrations for mAbs across different drugs, with an expected CSF:serum ratio of 0.1% to 0.2%. Lecanemab's PK profile is proposed to align with that of other mAbs, showing slow CSF concentration increase post intravenous administration and subsequent decrease with a serum like half-life.

Elimination

No absorption, distribution, metabolism and excretion (ADME) studies were conducted as per the guideline for antibodies. The mean terminal t½ of lecanemab was 5 to 7 days when administered at 1 mg/kg or higher doses.

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

Dose proportionality and time dependency

Dose proportionality

Serum lecanemab Cmax and AUC increased in an approximately dose-proportional manner within the assessed single dose range of 0.3 mg/kg to 15 mg/kg. The concentration-time profiles are characterised by a rapid distribution phase followed by a long terminal elimination phase. The mean terminal t½ of lecanemab was 5 to 7 days when administered at 1 mg/kg or higher doses.

Time dependency

Steady state after biweekly dosing was achieved after 3 to 4 doses with an accumulation ratio of approximately 1.5 based on AUC. CL and t½ of lecanemab were consistent across dose levels of 1 mg/kg or higher, and exposure increased dose-proportionally, suggesting linear PK. The accumulation ratio is consistent with the half-life.

Intra- and inter-individual variability

The calculated population estimate for CL stood at a modest 0.0154 L/h, exhibiting an inter-individual variability of 34.9%. Likewise, the appraisal of the central volume of distribution indicated a diminutive 3.24 L, accompanied by an inter-subject variability of 12.2%.

Pharmacokinetics in target population

A population PK analysis was conducted to identify intrinsic (e.g., age, sex, race) and extrinsic factors (manufacturing process/formulation) that explain between subject variability in lecanemab PK.

The population PK model was developed using pooled data from Studies 101, 104, 201 and 301 and included data from healthy subjects and patients receiving single and multiple lecanemab doses.

The final PK dataset used in the population PK analysis included 21929 serum lecanemab observations from 1619 subjects, after excluding lecanemab concentrations over 600 pg/mL, observations with time after dose (TAD) over 2000 hours and observations with CWRES > 5 identified in the development of the base PK model.

Of the 21929 PK samples 653 (3.0%) were from Study 101, 395 (1.80%) from Study 104, 7991 (36.4%) from Study 201 Core and OLE, and 12890 (58.8%) from Study 301 Core and OLE. Study 301 OLE observations included data from subjects who received 10 mg/kg both in the Core and OLE and only from 2 subjects who received placebo in 301 Core and 10 mg/kg in the OLE. Of the 21929 PK samples 8595 samples (39.2%) were Process A-1 from Studies 101, 104 and 201 Core and 13334 (60.8%) were Process B-1 from Studies 201 OLE and 301 Core and OLE. Of the 21929 PK samples 20704 samples (94.4%) were categorized as ADA negative at samples level (ADA negative, ADA negative inconclusive, ADA negative conclusive and unavailable) and 1225 samples (5.6%) as ADA positive at sample level (ADA positive, ADA positive induced and ADA positive boosted).

A total of 614 PK samples were excluded from the PK analysis. Of the 614 samples excluded 337 were with serum concentrations below the limit of quantification (BLQ) or BLQ with TAD over 2000 hours, 61 with missing PK sampling time, 107 with CWRES > 5, 46 with serum concentrations above 600 µg/mL, considered as outliers as these observations are inconsistent within the same subject's profiles and are much higher than those for other

subjects, and 30 with TAD over 2000 hours, which is more than 10-fold the average elimination half-life of 7 days.

A sensitivity analysis assessed the impact of concentrations >600 μg/mL and showed similar model parameters with these individuals included.

Similar to other monoclonal antibodies, the PK of lecanemab is well described by a two-compartment base model with zero-order input and first order elimination from the central compartment. The model was parameterised for clearance (CL), central and peripheral volumes of distribution (V1 and V2, respectively) and inter- compartmental clearance (Q). To account for differences in PK associated with manufacturing processes, the bioavailability of Process B-1 relative to Process A-1 (F1) was also added to the model.

Based on model development a model parameterised for CL, V1, V2, Q, and bioavailability of Process B-1 relative to Process A-1 (F1), a model with exponential inter-individual variability (IIV) estimated for all parameters, except for Q, with a covariance between CL and V1, and a combined (proportional and additive) residual variability error model was selected as the base PK model for lecanemab. All key model parameters were estimated with good precision (%RSE < 4.30%).

Univariate Analysis was initially performed for the Lecanemab PK Model. The Eta shrinkage in the base PK model was 6.05% for CL, 21.2% for V1, 30.0% for V2 and 53.3% for F1. Thus, univariate analysis was performed for the effect of covariates on CL, V1 and V2, except for liver function biomarkers (ALT, AST and ALP), total bilirubin, and creatinine clearance (CrCL) since monoclonal antibodies (mAbs) are not metabolised by liver and elimination of mAbs through the kidney is considered insignificant.

In all covariate analyses, each significant covariate from the univariate analysis at $p \leq 0.01$ (ΔOFV >6.64 [1 df]) was carried forward in the model and removed in the backward elimination step if the p value was > 0.001.

All key model parameters of the structural model were estimated with good precision (%RSE<4.30%). The confidence intervals from nonparametric bootstrap are narrow and the median values of the distribution of bootstrapped parameter values are consistent with the parameter estimates from the final PK model. Overall, the bootstrap results indicated that the final PK model for lecanemab was valid and stable and produced well estimated parameters.

The final population PK model for lecanemab contained statistically significant covariate effects of ADA status as time-variant, body weight, albumin, and sex on CL; sex, Japanese race/ethnicity and body weight on central volume of distribution; and Japanese race/ethnicity on peripheral volume of distribution ADA titer, age, race/ethnicity, liver function biomarkers (ALT, AST, ALP and total bilirubin), and creatinine clearance had no significant effects on CL.

Goodness-of-fit-plots for the final PK model for lecanemab showed even distribution around the line of unity. The scatter plot of CWRES versus population predicted concentrations and versus time showed the CWRES to be evenly distributed around zero, supporting the validity of the PK model.

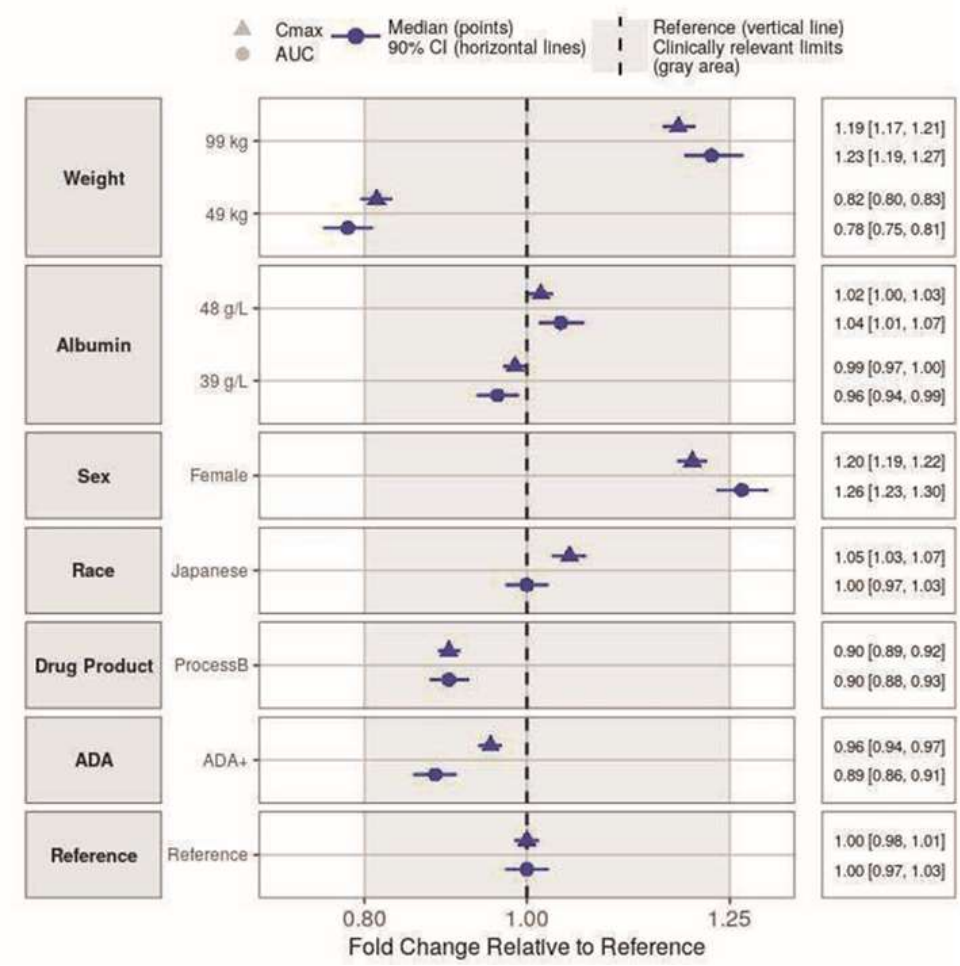
The effect of significant covariates on lecanemab AUC and Cmax at steady state after 10 mg/kg bi-weekly dosing of lecanemab are shown as a forest plot in Figure 5. This plot

displays a change in steady state AUC and Cmax with 90% CI for each covariate relative to the reference subject defined a 72 kg male, non-Japanese subject with albumin of 43 g/L who was administered Process A-1 drug product and all PK samples are ADA negative.

As shown in Figure 4, albumin and race/ethnicity have minimal or no effect on exposure of lecanemab. Females have on average 26% higher AUC than males. ADA positivity decreases AUC of lecanemab by 11%. As expected for a weight-based dosing, relative to an average subject of 72 kg, a subject with a low (5th percentile of PK dataset) body weight (49 kg) has 22% lower AUC, while for a subject with high (95th percentile of PK dataset) body weight (99 kg) the AUC is 23% higher. The estimated bioavailability for drug produced by Process B-1 relative to Process A-1 is 90%, with confidence interval within the 80-125% range.

Overall, none of the covariates which were found significant for PK of lecanemab are considered to have a clinically meaningful effect on lecanemab exposure.

Figure 4: Effect of Significant Covariates on Lecanemab AUC and Cmax at Steady State after 10 mg/kg Bi-Weekly

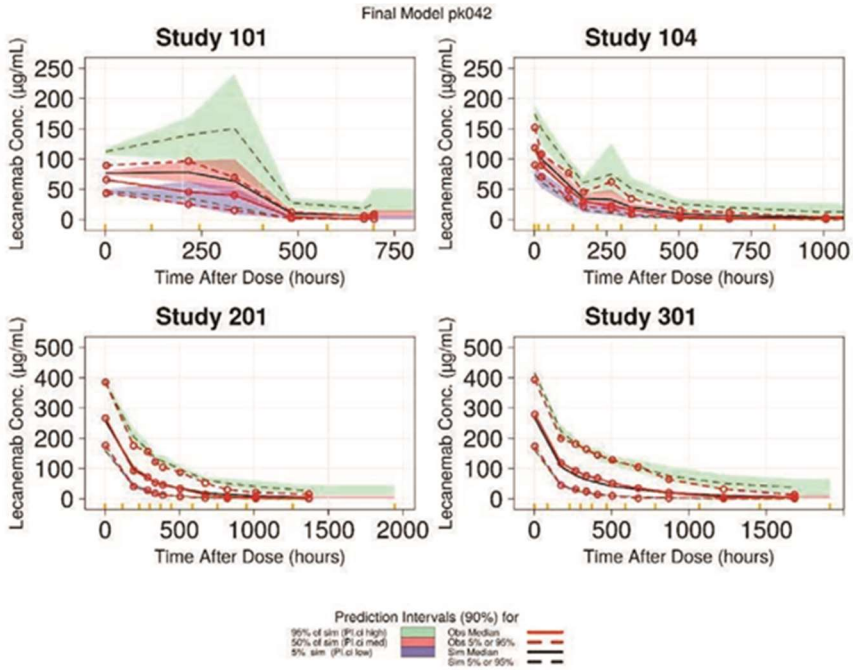


Visual Predictive Checks for Final PK Model

Model-predicted 5th, 50th and 95th percentiles were calculated based on the simulated data and plotted with 5th, 50th and 95th percentiles of observed lecanemab concentrations stratified by study, as depicted below in Figure 5. Based on the pcVPC plots, median and 95% prediction intervals of the observed concentrations are comparable to those from the simulations. Therefore, the lecanemab concentration time course has been well defined by the

final PK model with good predictive performance.

Figure 5: Prediction-Corrected Visual Prediction Check Plots for Final Lecanemab PK Model Stratified by Study.



The bioavailability of Process B-1 relative to Process A-1 was added to model on F1 to account for differences in PK associated with manufacturing process. Considering that Lecanemab is administered IV, adding process material on Clearance could be more appropriate. Models that might provide a more physiologically plausible relationship between lecanemab PK and manufacturing process were, therefore, explored. Models were tested that added manufacturing process as a covariate on clearance (CL), central volume of distribution (V1), and/or peripheral volume of distribution (V2). The model containing manufacturing process covariate on both V1 and V2 resulted in the lowest objective function value (OFV). This result suggests that manufacturing process affects volume of distribution without any effect on lecanemab CL. This model produced results comparable to the previous model. Importantly, transitioning from Process A to Process B material is projected to have no effect on AUC and a modest 8% reduction in Cmax.

Special populations

Impaired renal function
Based on population PK modelling, renal function was not a statistically significant covariate on the PK of lecanemab.

Impaired hepatic function
Based on population PK modelling, hepatic function was not a statistically significant covariate on the PK of lecanemab.

Gender
Report CPMS-BAN2401-002R-v1.1, -002R-ADD1-v1:
Out of the total study population of 725 individuals, 340 (approximately 47%) were female, and 385 (approximately 53%) were male. Sex was identified as a statistically significant covariate in both the first and second models. In the first model, the estimated ratio for sex on

CL was 0.786, indicating that there was a difference in CL between the two sexes. Similarly, in the first model, the estimated ratio for sex on the volume of the central compartment (V1) was also 0.786, suggesting a sex-related difference in V1. In the second model, the estimated ratio for sex on clearance (CL) was 0.792, indicating a similar finding of a significant effect of sex on CL. Additionally, in the second model, the estimated ratio for sex on the volume of the central compartment (V1) was 0.893, again suggesting a significant influence of sex on V1.

Report CPMS-BAN2401-003R1-v1
In the study population of 1,619 individuals, a total of 800 (approximately 49.4%) were female, while 819 (approximately 50.6%) were male. The analysis revealed that sex was identified as a statistically significant covariate in the study. Specifically, the estimated ratio for sex on CL was 0.791, indicating a significant effect of sex on CL. Additionally, the estimated ratio for sex on the volume of the central compartment (V1) was 0.868, suggesting that sex also had a significant impact on V1.

Several factors, including body weight, glomerular filtration, muscle mass, and plasma volume, are suggested to contribute to the sex-based variability. Non-clinical studies may suggest that gender-related hormones may modulate the expression and function of the FcRn receptor, offering a potential explanation for the observed differences.

Race
Among the study population (n=1619), overall, 1307 (80.7 %) were White, 48 (3 %) Black/African American, 21 (1.3 %) Asian (non-Chinese, non-Japanese), 138 (8.5 %) Japanese, 6 (0.4 %) Chinese, 54 (3.3 %a) Korean, and 45 (2.8 %) of other races. Japanese race/ethnicity was identified a statistically significant covariate on CL (estimate=0.920) and on peripheral volume of distribution (estimate=0.671).

Based on the current population PK modelling, Japanese patients are expected to have a lower CL and volume of distribution (peripheral) leading to a higher exposure compared to non-Japanese patients. However, these differences are not significant.

Weight
Among the study population (n=1619), overall mean body weight was 72 kg ranging from min=37.7 kg to max=130.5 kg. Body weight was identified as a statistically significant covariate on CL (exponent=0.353) and on central volume of distribution (exponent=0.513).

The modelled exponents for CL and volume of Vd based on body weight were approximately half of the expected physiological values. The company suggests that deviations in exponents are not uncommon in modelling and the inclusion of sex as a covariate, which correlates with body weight, impacted the exponents.

Lecanemab has been administered based on weight in all clinical studies, contributing to a substantial safety database with diverse body weights.

Elderly
Among the study population (n=1619), overall mean age was 72 years ranging from min=50 years to max=93 years. During population PK modelling, age was not identified as statistically significant covariate on any PK parameter.

Children
Paediatrics are not part of the target population and no data in paediatrics are available.

Albumin level
Among the study population (n=1619), overall mean albumin was 43 g/L ranging from min=35 g/L to max=54 g/L. Albumin was identified as a statistically significant covariate on CL (estimated exponent =-0.374) resulting in a decrease in CL with increasing albumin.

Based on the current population PK modelling, patients with higher albumin level are expected to have slightly higher exposure and those with lower albumin level are expected to have slightly lower exposure compared to the typical patient.

Immunogenicity
Among the study samples (n=21929), 1225 were ADA positive and 20704 ADA negative. In the Phase 3 study, overall, out of 12890 samples, 12715 were ADA negative and 174 were ADA positive. ADA status was identified as a statistically significant covariate on CL (ratio = 1.13). Individual study data confirm these conclusions.

The current bioanalytical method for ADAs has a limited drug tolerance level of 31.3 µg/mL for Lecanemab. A significant portion of ADA samples from these trials exceeded this threshold, leading to their classification as "negative inconclusive". It is also noted that in study 201-CORE, no subjects were classified as ADA negative inconclusives, and ADA positivity was significantly higher (43.3%) compared to other clinical studies, such as 201-OLE (5.5%) and 301-CORE (5.1%) studies.

The applicant has advised that a more sensitive ADA assay with an increased drug tolerance is currently in development. The applicant is proposing to submit a reanalysis of the samples from study 301 core in late 2025. Provision of this new data, together with a re-evaluation of any impact of immunogenicity on efficacy, safety and PK is a post-authorisation commitment.

Overall conclusions on special populations
A population PK analysis has been provided to inform on the effect of intrinsic and extrinsic factors. Based on population PK modelling, renal and hepatic function were not statistically significant covariate on the PK of lecanemab. A sex difference is apparent in the pharmacokinetics and females are expected to have lower CL and Vd, Japanese patients are also expected to have a lower CL and volume of distribution leading to a higher exposure compared to non-Japanese patients. Age (50 to 93 years) was not identified to affect the PK of lecanemab. Patients with higher albumin level are also expected to have slightly higher exposure. However, none of these differences are expected to be significant. Body weight affects CL and volume of distribution, the exponents are not close to those normally expected on a physiological basis. It is acknowledged, however, that Lecanemab has been administered based on weight in all clinical studies, contributing to a substantial safety database with diverse body weights.

Pharmacokinetics interactions studies
Pharmacokinetic drug interactions are not expected and have not been observed in the clinical studies.

Exposure relevant for safety evaluation
Lecanemab PK Parameters after the 1st and last Intravenous Administration 10 mg/kg

biweekly in Study 101 are shown in Table 7 below.

Table 7: Lecanemab PK Parameters after the 1st and Last Intravenous Administration 10 mg/kg biweekly in Study 101

Dose Level, (mg/kg)[a]	Dose Day	In-fusion No.	C_{max} (µg/mL)		t_{max} (hours)	$AUC_{(0\text{-}24h)}$ (µg·h/mL)		$AUC_{(0\text{-}\tau)}$ (µg·h/mL)		$t_{½}$ (hours)
			Mean (SD)	CV%	Median (min, max)	Mean (SD)	Mean (SD)	Mean (SD)	CV%	
MAD4 (10) Biweekly	1	1	267 (61.8)	21.1	1.67 (1.27, 3.08)	4750 (1210)	23.9	27,200 (8820)	30.5	105 (22.1)
	84	7	307 (70.2)	21.5	1.88 (1.13, 3.10)	5720 (1230)	19.6	37,700 (9110)	25.5	127 (29.9)

Overall conclusions on pharmacokinetics

The clinical pharmacology package consists of 8 ongoing or completed studies in 2203 lecanemab-treated subjects and 1300 placebo-treated subjects with EAD (placebo [n=1142], lecanemab [n=2045]) and preclinical AD (placebo [n=158], lecanemab [n=158]). Three of the 8 studies are completed Phase 1 studies that evaluated single or multiple doses of lecanemab, (0.1 to 15 mg/kg) administered to subjects with mild to moderate AD (BAN2401 A001 101) and MCI due to AD and mild AD (BAN2401 J081 104) and Study BAN2401-A001-004. There is 1 large, dose-range finding, Phase 2 study and 1 large confirmatory Phase 3 study in subjects with EAD. Study 201 is a Phase 2 study with a Core and an Open-label Extension (OLE) Phase and Study 301 is a Phase 3 study with a Core and an OLE Phase. Study 301 Core and Study 201 Core have completed; the 301 OLE Phase and 201 OLE Phase are ongoing. A Phase 3 study (BAN2401-G000-303) in subjects with preclinical AD, and a Phase 2/3 study (DIAN-TU-001) in subjects with Dominantly Inherited Alzheimer's Disease (DIAD) are also ongoing.

The mean terminal t1/2 of Lecanemab was 5 to 7 days when administered at 1 mg/kg or higher doses. Studies 101 and 104 show dose-proportional exposures of Lecanemab in the 0.3 to 15 mg/kg range. Steady state after biweekly dosing was achieved after 3 to 4 doses with an accumulation ratio of approximately 1.5 based on AUC. The accumulation ratio is consistent with the half-life. Comparability between the to-be marketed formulation, C2, and other formulations used in the Clinical Pharmacology studies has been sufficiently presented.

Plasma protein binding is low, and the volume of distribution is low, as expected. CSF concentrations were measured in two phase 1 clinical studies and demonstrated variability but fell within the range of the larger Study 301 Core dataset.

A population PK analysis has been provided to inform on the effect of intrinsic and extrinsic factors and to support the PKPD modelling. Based on population PK modelling, renal and hepatic function were not statistically significant covariates on the PK of lecanemab. Gender, race and albumin are expected to have an effect on exposure, however, none of these differences are expected to be significant.

Lecanemab has been administered based on weight in all clinical studies, contributing to a substantial safety database with diverse body weights.

Pharmacokinetic drug interactions are not expected and have not been observed in the clinical studies.

IV.3 Pharmacodynamics

Data was used from all clinical studies in a large number of PKPD models based on biomarkers and efficacy end points.

- Study BAN2401-A001-101 (Study 101) was conducted in subjects with clinical diagnosis of probable mild to moderate AD.
- BAN2401-J081-104 (Study 104)
- Study BAN2401-A001-004 (Study 004)
- BAN2401-G000-201 (Study 201)
- BAN2401-G000-301 (Study 301).

Primary pharmacology

Lecanemab selectively targets large soluble protofibrils relative to monomers (greater than 1000-fold selectivity over Aβ monomers), with preferential activity over insoluble fibrils (up to 10-fold over fibrils).

In vitro studies revealed that lecanemab selectively binds to Aβ protofibrils with IC50 values of 0.56 to 3.3 nmol/L (84–495 ng/mL), aligning with observed CSF concentrations in clinical studies. However, the applicant suggests the primary evidence for the efficacy of the 10 mg/kg biweekly regimen in early Alzheimer's disease comes from clinical studies. A recently developed quantitative systems pharmacology model, incorporating ADNI data and Studies 201 and 301, predicts clinical and biomarker effects of lecanemab. The model suggests that at 10 mg/kg biweekly, substantial reductions in protofibril concentrations are expected. This gives support to lecanemab reducing protofibril concentrations at the proposed dose, but the link to slowing disease progression is limited.

The effect of lecanemab to reduce brain amyloid was measured using amyloid positron emission tomography (PET) imaging. Since clearance (CL) of brain amyloid may alter the dynamics of Aβ aggregation and result in changes in levels of total Aβ monomers, changes in Aβ levels were also explored in plasma to support target engagement of lecanemab. Evidence of drug-related effect on downstream AD pathophysiology was further explored using biomarkers, including plasma human tau protein phosphorylated at threonine in position 181 (p-tau181) as a biomarker of tau pathology. A beneficial drug-related effect would be a reduction or slowdown of accumulation of these pathophysiological biomarkers that are downstream of brain amyloid pathology.

Statistically significant reductions of Aβ-positive plaques were also observed in mouse studies.

Secondary pharmacology

The potential for off-target binding was explored in plasma from rat, mouse, monkey, healthy human subjects, and AD subjects. A 150 kDa band immunoprecipitated from human plasma was identified as thrombospondin 1 (THBS1). The equilibrium constant (KD) was determined to be 4 μmol/L.

Immunogenicity risk of lecanemab was evaluated using ex vivo screening technology. Lecanemab induced a low frequency of positive responses with a combined assay response rate of 8%, reflective of a low predictive risk of clinical immunogenicity.

The potential for microhaemorrhage was also investigated in Tg-APPArcSwe mice and Tg2576 mice, and no treatment-related microhaemorrhages in the brain were observed in any of these studies.

Pharmacodynamic interactions with other medicinal products or substances
In studies 301 and 201, concurrent use of symptomatic treatments for AD (e.g. donepezil, rivastigmine, galantamine, tacrine, and memantine) was allowed. The treatment-emergent adverse events (TEAEs) in subjects receiving lecanemab 10 mg/kg biweekly and those on a placebo were similar, irrespective of whether they were concurrently using approved AD treatment. The simultaneous utilisation of approved symptomatic AD treatment did not seem to influence the frequency of ARIA-E.

In Study 301 Core, no disparities in the incidence of ARIA-E were observed when used alongside antithrombotic agents, including antiplatelets, anticoagulants, and thrombolytics. When antithrombotic agents were used concurrently, the rate of ARIA-E was 6 out of 311 (1.9%) for placebo and 74 out of 564 (11.7%) for lecanemab 10 mg/kg biweekly. In cases where antithrombotic agents were not used concurrently, the incidence of ARIA-E was 9 out of 586 (1.5%) for placebo and 74 out of 564 (13.1%) for lecanemab 10 mg/kg biweekly.

The risk of macrohaemorrhages is higher in individuals using both lecanemab 10 mg/kg biweekly and anticoagulants, but it is uncertain to what extent lecanemab 10 mg/kg biweekly contributes to this risk, as anticoagulants alone confer a greater risk of macrohaemorrhage in non-AD populations. The risk in AD populations with Cerebral Amyloid Angiopathy (CAA) is unknown at present but is expected to be elevated. Consequently, any additional risk cannot be definitively assessed.

At present it is considered that the risk of intracerebral haemorrhage with lecanemab treatment in patients treated with concomitant antithrombotic medication, particularly anticoagulants or a thrombolytic agent is not well characterised, and an increased risk cannot be excluded.

An appropriate contraindication and warnings regarding concomitant use of lecanemab and anticoagulants or thrombolytic agents are included in the SmPC.

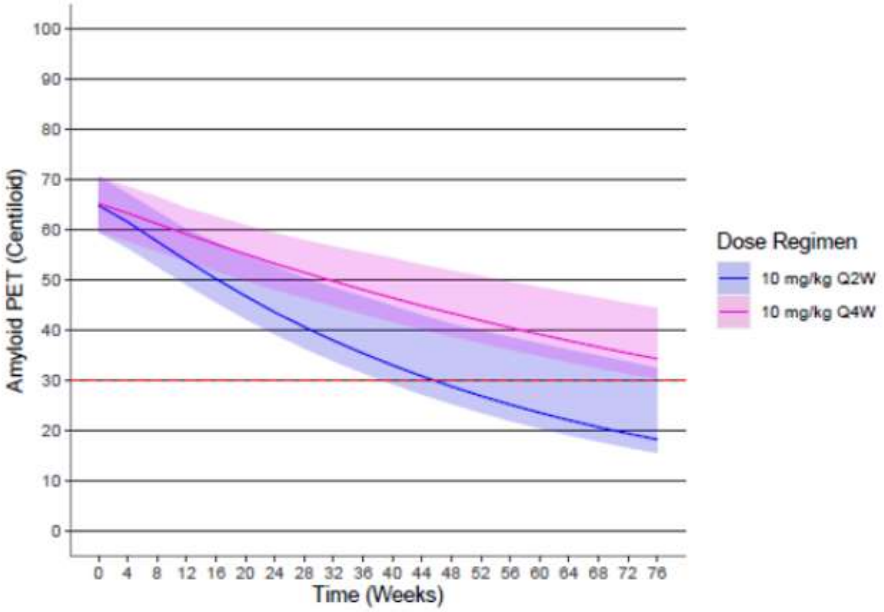
Genetic differences in pharmacodynamic response
The effect of ApoE4 genotype was explored in all PKPD and exposure response analysis for efficacy and safety. ApoE4 carrier status has a significant effect on baseline amyloid and safety measured by ARIA-E.

Relationship between plasma concentration and effect
<u>PKPD for Amyloid PET using Centiloids</u>
A model was developed to describe the relationship between drug concentration and Amyloid PET signal. For the PK/PD analysis of amyloid PET, subjects receiving lecanemab with serum PK information or receiving placebo in studies 301 Core and OLE and 201 Core and who had baseline and at least one postdose PET assessment were included. Subjects treated with lecanemab 10 mg/kg biweekly in Study 201 OLE and who had baseline amyloid PET assessment were also included. The PK/PD dataset included 4129 observations from 1088 subjects who were on treatment, of which there were 2332 observations from 622 subjects assigned lecanemab and 1797 observations from 466 subjects assigned placebo. The relationship between serum lecanemab concentration and the amyloid PET reduction time course was best described by an indirect response model with lecanemab-dependent reduction of amyloid plaque.

The signal was predicted to decline more quickly in subjects with higher lecanemab exposure

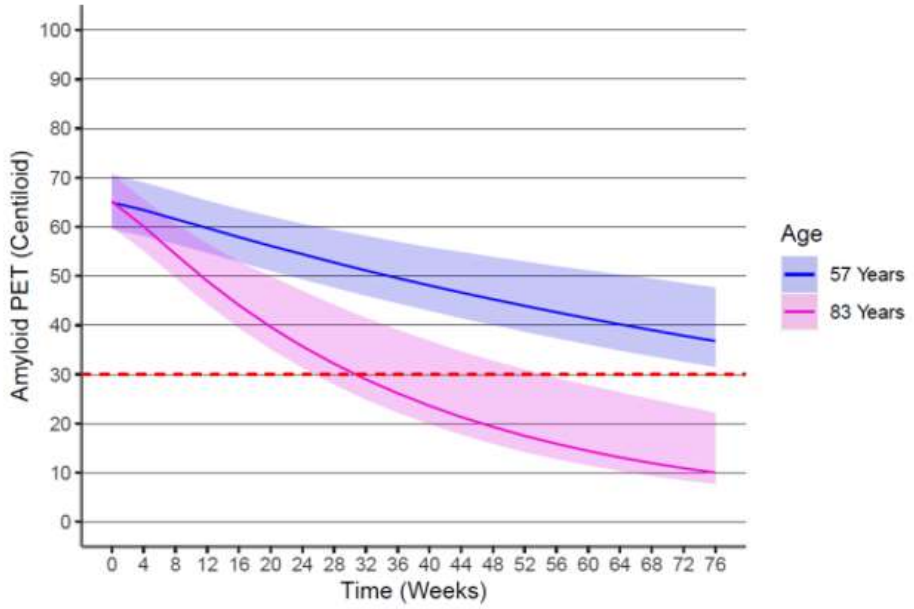
(figure 6). The model showed that over 18 months the lecanemab 10 mg/kg biweekly dose resulted in a larger and faster decrease in PET signal as compared to lecanemab 10 mg/kg monthly. The average subject on lecanemab 10 mg/kg biweekly dose was predicted to achieve amyloid negativity (<30 Centiloids) after 18 months of treatment.

Figure 6: Model-Predicted Amyloid PET following 18 months treatment with LEC10-BW or LEC10-M in APOE Noncarriers



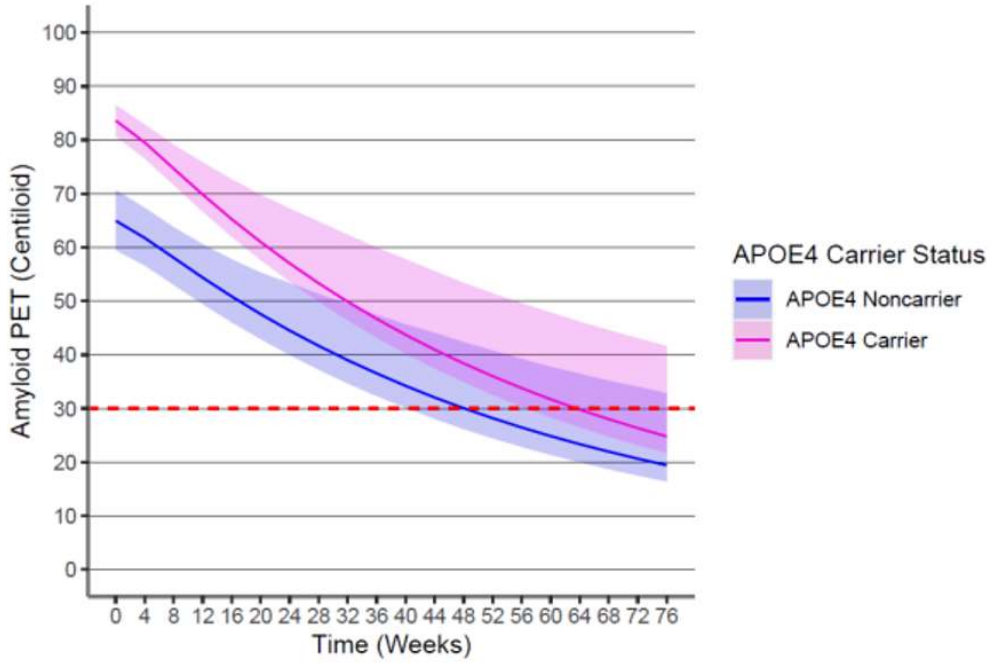
To demonstrate the effect of age on the rate of amyloid CL, the model was used to predict amyloid PET profiles over 18 months of treatment with lecanemab 10 mg/kg biweekly for subjects representing the 5th (57 years) and 95th (83 years) percentiles of age in the PK/PD (figure 7). A typical 83-year-old subject is predicted to achieve amyloid negativity (<30 Centiloids) by approximately 32 weeks of treatment. A typical younger 57-year-old subject would require longer than 18 months of treatment to achieve amyloid negativity.

Figure 7: Model-Predicted Amyloid PET following 18 months treatment with LEC10-BW in Younger (57 years) or older (83 years) APOE Noncarriers



An effect of ApoE4 carrier status on baseline amyloid was found (figure 8). For ApoE4 noncarriers, the estimated baseline amyloid level was 65 Centiloids, while for ApoE4 carriers, the value was 83 Centiloids. To demonstrate the effect of ApoE4 carrier status, change in brain amyloid removal over 18 months of treatment with LEC10-BW was simulated for ApoE4 carriers and ApoE4 noncarriers. The higher baseline level of amyloid resulted in a faster initial rate of removal in ApoE4 carriers; however, at the end of the 18-month treatment period, amyloid levels were similar.

Figure 8: Model-Predicted Amyloid PET following 18 months treatment with LEC10-BW by APOE carrier status.



The t½ of amyloid re-accumulation is estimated to be approximately 14 years, based on the final population estimate of Kout.

Exposure-Response Analysis for Plasma Aβ42/40 Ratio

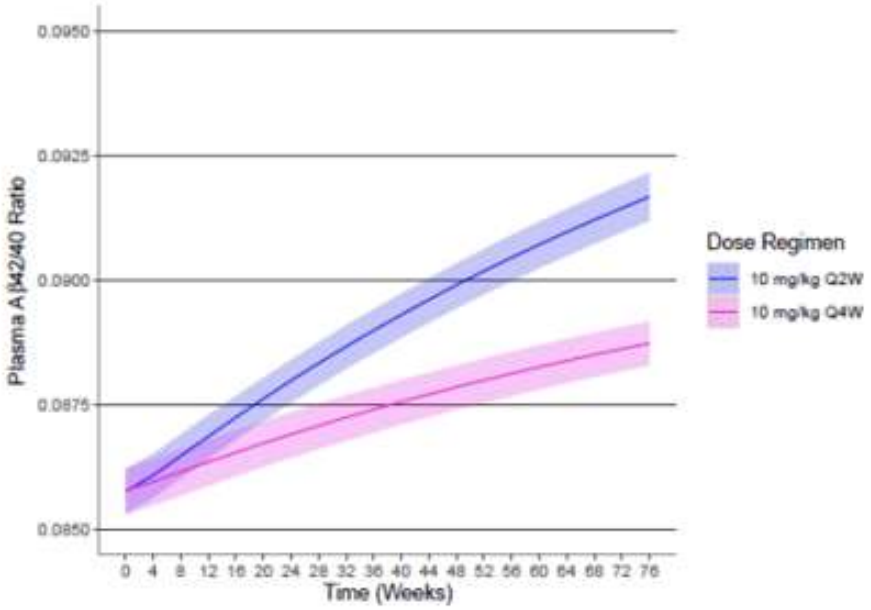
A model was developed to describe the relationship between drug concentration and plasma Aβ42/40. Plasma Aβ42/40 has been shown in the literature to correlate with brain amyloid; treatment aimed toward reducing brain amyloid is expected to increase plasma Aβ42/40.

For PK/PD analysis of the plasma Aβ42/40 ratio, all subjects receiving lecanemab with serum PK information or receiving placebo in Study 301 Core and OLE Phase and Study 201 Core and who had baseline and at least one postdose Aβ42/40 ratio assessment were included. Subjects treated with lecanemab 10 mg/kg biweekly in Study 201 OLE Phase and who had baseline and postdose Aβ42/40 ratio assessment were also included.

In total, there were 7544 observations from 1961 subjects with the majority of Aβ42/40 ratio observations from subjects receiving placebo (43.7%) and lecanemab 10 mg/kg biweekly (47.2%) during Study 301 Core and Study 201 Core. Absolute plasma Aβ42/40 ratio over time (R[t]) was described as a function of PK model-predicted lecanemab serum concentration at the time of the assessment. The relationship between lecanemab concentration and plasma Aβ42/40 ratio change was described by an indirect response model with lecanemab concentration as a linear function of increasing plasma Aβ42/40 ratio.

Plasma Aβ42/40 ratio was predicted to increase more quickly in subjects with higher lecanemab exposure. Figure 9 shows model-predicted plasma Aβ42/40 ratio vs time profiles for lecanemab 10 mg/kg biweekly and lecanemab 10 mg/kg monthly treatment for 18 months, indicating that the lecanemab 10 mg/kg biweekly dose resulted in a larger and faster increase in Aβ42/40 ratio with time than lecanemab 10 mg/kg monthly.

Figure 9: Model-Predicted Plasma Aβ42/40 ratio after 18 months of treatment with LEC10-BW and LEC10-M



The effect appears relatively small over placebo, particularly in study 201. In addition, the time to re-accumulation was much shorter than for brain. With respect to the clinical relevance of the changes in plasma biomarkers, Aβ42/40 ratio levels are known to be altered in Alzheimer's disease (AD) patients. Plasma Aβ42/40 has been shown to predict amyloid PET levels in the literature, with lower ratios associated with greater amyloid PET signal. Accordingly, the increase in Aβ42/40 ratio associated with lecanemab administration can reasonably be thought to reflect lecanemab efficacy through reduced brain amyloid.

Exposure-Response Analysis for Plasma p tau181

A model was developed to describe the relationship between drug concentration and plasma P-tau181. P-tau181 is a biomarker of fibrillary tau that correlates with tau pathology.

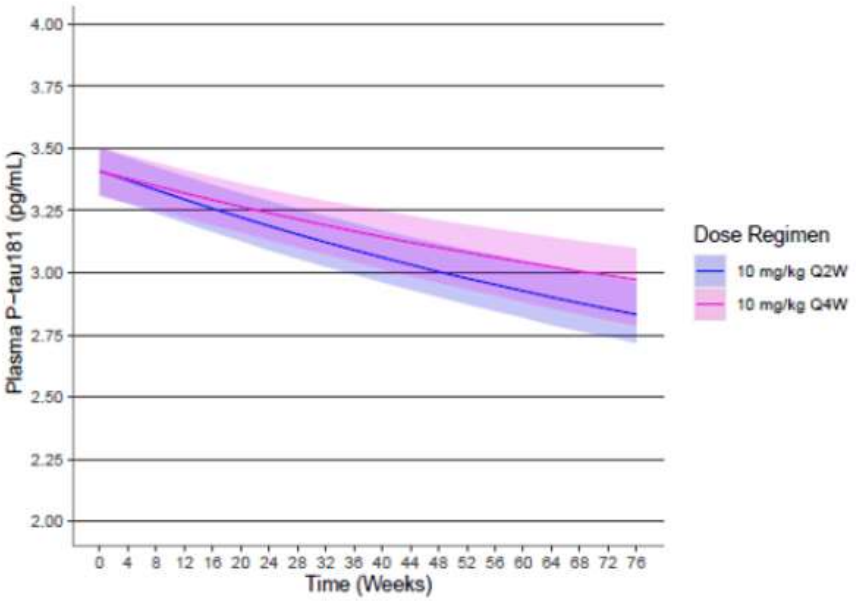
All subjects receiving lecanemab with serum PK information or receiving placebo in studies 301 Core and OLE Phase and 201 Core and OLE Phase and who had baseline and at least 1 postdose p-tau181 assessment were included in PK/PD analysis of plasma p-tau181. Subjects treated with LEC10-BW in Study 201 OLE Phase and who had baseline and postdose p-tau181 assessment were also included. There were 7909 observations from 2179 subjects with the majority of p-tau181 observations from subjects receiving placebo (42.5%) and lecanemab 10 mg/kg biweekly (43.6%) during the Core of studies 201 and 301.

Absolute plasma p-tau181 measurements over time (R[t]) were related to model-predicted lecanemab serum concentration at the time of the assessment. A high plasma p-tau181 is indicative of elevated amyloid in the brain; therefore, treatment aimed toward reducing brain amyloid was expected to decrease the plasma p-tau181. The relationship between lecanemab

concentration and the p-tau181 change time course was best described by an indirect response model with the lecanemab concentration as an Emax function decreasing the plasma p-tau181 formation.

Plasma p-tau181 is expected to decrease more quickly in subjects with higher lecanemab exposure. Figure 10 shows model-predicted p-tau181 vs time profiles for lecanemab 10 mg/kg biweekly and lecanemab 10 mg/kg monthly treatment for 18 months, indicating that the lecanemab 10 mg/kg biweekly dose results in larger decrease in p-tau181 after 18 months of dosing than lecanemab 10 mg/kg monthly.

Figure 10: Model-Predicted Plasma p-tau181 after 18 months of treatment with lecanemab 10 mg/kg biweekly and lecanemab 10 mg/kg monthly

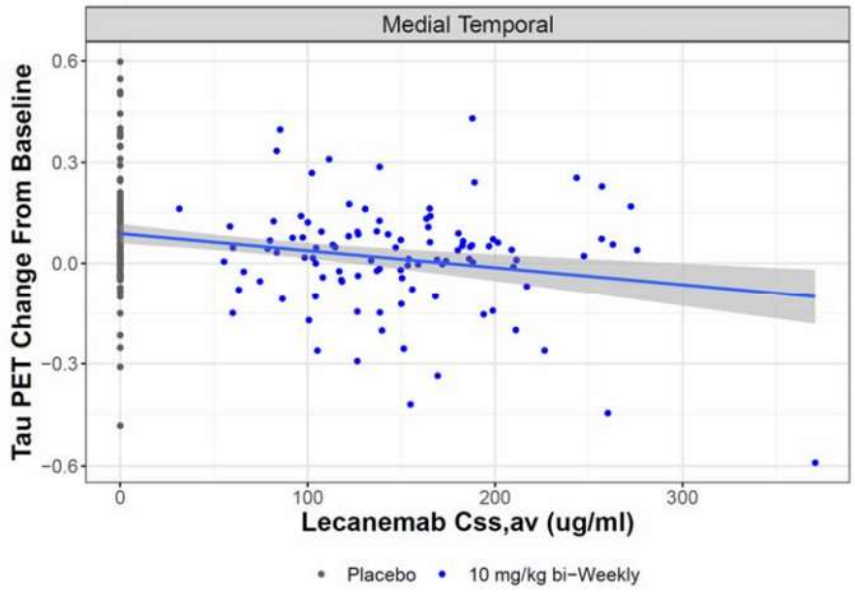


The effect appears relatively small over placebo, particularly in study 201. In addition, the time to re-accumulation was again much shorter than for brain. In plasma, p-tau181 could be reasonably assumed to reflect a reduction in brain amyloid and associated neuritic dystrophy and tau deposition, however the lack of understanding of PKPD currently limits its usefulness as a biomarker.

Exposure-Response Analysis for Tau PET

Tau PET standard uptake value ratio (SUVr) was obtained from a total of N=364 subjects from Study 301 Core, with 179 placebo subjects and 185 lecanemab 10 mg/kg biweekly treated subjects. Graphical analysis for the CFB in tau PET (Medial Temporal) as a function of CFB in brain amyloid at 18 months post treatment suggested that tau accumulation during 18 months of lecanemab treatment appeared to be slower for subjects with greater amyloid removal. Following placebo, the tau PET generally increased from baseline at 18 months. A relationship is proposed with Css,ave, however again the effect appears small (Figure 11).

Figure 11: Individual Change from baseline in Tau PET SUVr versus Model-Predicted Steady-State Lecanemab Exposure



Exposure-Response Analysis for Efficacy Endpoints (CDR-SB and ADAS-Cog14)

The objectives of exposure-response analyses were to:

- describe the natural progression of the disease as characterised by CDR-SB or ADAS Cog14 in placebo-treated subjects
- quantify the relationship between lecanemab exposure and CDR-SB and ADAS-Cog14
- evaluate the factors contributing to the inter-subject variability of the response.

Subjects receiving lecanemab or placebo in studies 301 Core and 201 Core and who had at least 1 post-dose CDR-SB and ADAS-Cog14 assessments were included in the analysis.

For CDR-SB, there were 11,140 observations from 1734 subjects in Study 301 Core and 4998 observations from 828 subjects in Study 201 Core. In total, there were a total of 16138 observations for CDR-SB from 2562 subjects, of which 8979 observations were from 1448 subjects receiving lecanemab and 7159 observations were from 1114 subjects receiving placebo.

For ADAS-Cog14, there were 11065 observations from 1734 subjects in Study 301 Core and 4955 observations from 827 subjects in Study 201 Core. In total, there were a total of 16,020 observations for ADAS-Cog14 from 2561 subjects, of which 8907 observations from 1448 subjects receiving lecanemab and 7113 observations were from 1113 subjects receiving placebo.

A linear disease progression model, estimating baseline clinical score (BASE) and a slope of disease progression (SLP) was developed using placebo data to describe the disease progression of CDR-SB and ADAS-Cog14 over time.

The disease progression models included the following significant covariates:

- CDR-SB: race (Asian vs Others) and clinical subgroup (mild AD vs MCI) on baseline, and clinical subgroup and AD symptomatic medication on disease

progression rate. There were no additional significant effects of age, sex, and ApoE4 carrier status.

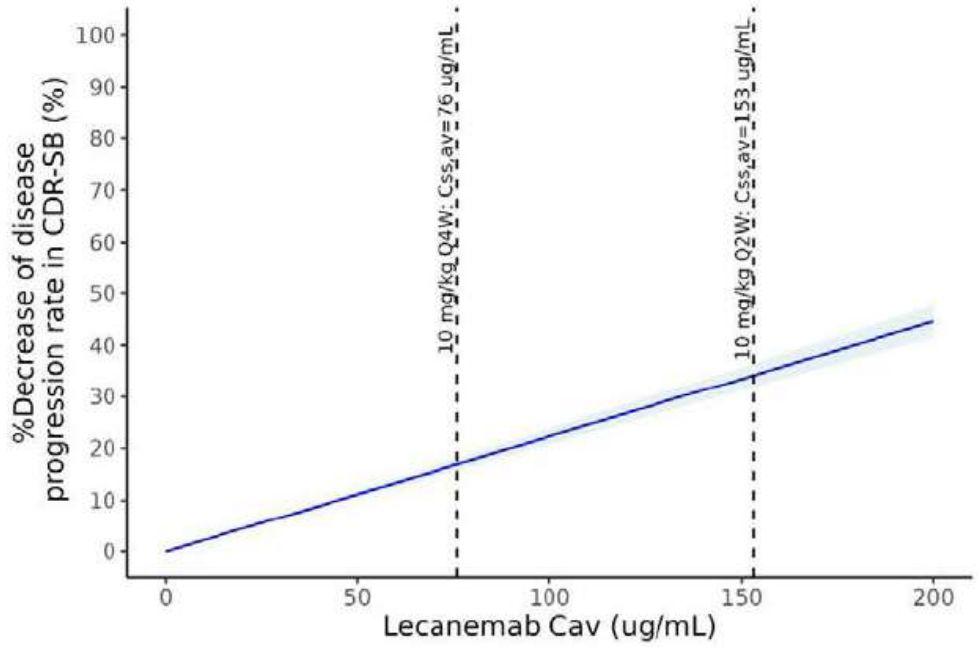
- ADAS-Cog14: age, race (Asian vs Others), clinical subgroup (mild AD and MCI), AD symptomatic medication on baseline, and clinical subgroup and AD symptomatic medication on disease progression rate. There were no additional significant effects of sex, and ApoE4 carrier status.

For each clinical endpoint, a PK/PD model was developed introducing lecanemab exposure effect on the disease progression (EFF) with covariates effect on baseline clinical score (BASE), and disease progression rate (SLP).

Css,av resulted in the largest reduction in the objective function value (OFV) and was selected as the lecanemab exposure parameter for PK/PD models of both CDR-SB and ADAS-Cog14.

Significant covariates identified in the final PK/PD model for CDR-SB indicated that Asian subjects had 10% lower baseline CDR-SB than other subjects, mild AD subjects had 53% higher baseline CDR-SB and 50% faster disease progression rate than MCI subjects. Subjects with AD symptomatic medication at baseline had 67% faster disease progression rate than subjects without AD symptomatic medication at baseline. After accounting for other covariates, ApoE4 carrier status did not significantly affect the disease progression rate for CDR-SB. Covariate effects could not be tested on lecanemab exposure effect as Eta shrinkage for this parameter in the base PK/PD model was above 30%. Median lecanemab Css,av in subjects who received lecanemab 10 mg/kg biweekly in Study 301 Core was 153 µg/mL. The associated model-predicted decline in disease progression was 34.2% (95% CI: 31.8% – 36.5%).

Figure 12: Relationship between Lecanemab and Predicted Percent Decrease in Disease Progression Rate in CDR-SB



Line and area represent mean and 95% confidence interval.
CDR-SB = Clinical Dementia Rating – Sum of Boxes, Cav = average plasma concentration.

Significant covariates identified in the final PK/PD model for ADAS-Cog14 were: Asian subjects had 13% higher baseline ADAS-Cog14 than other subjects. Baseline ADAS-Cog14 score increased with age. Mild AD subjects had 19% higher baseline ADAS-Cog14 and 58% faster disease progression rate than MCI subjects. Subjects with AD symptomatic medication at baseline had 11% higher baseline ADAS-Cog14 and 79% faster disease progression rate than subjects without AD symptomatic medication at baseline. There were no significant effects of age, sex, weight, race/ethnicity, and ApoE4 carrier status on disease progression rate.

The PK/PD model predicted an exposure-dependent slowing of cognition decline on ADAS-Cog14. Covariate effects could not be tested on lecanemab exposure effect for ADAS-Cog14 as Eta shrinkage for this parameter in the base PK/PD model was above 30%. For median lecanemab Css,av in subjects who received lecanemab 10 mg/kg biweekly in Study 301 (153 µg/mL), the associated model-predicted decline in disease progression was 31.0% (95% CI: 25.2 – 36.8%) for ADAS-Cog14.

Exposure-Response Relationships for Safety (ARIA-E and Isolated ARIA-H)
A logit model describing the incidence of ARIA-E as a function of lecanemab exposure was developed with PK model-predicted exposure parameters.

Css,max was selected the best predictor of incidence of ARIA-E for the base model and the subsequent univariate analysis. Age, body weight, race/ethnicity, sex, baseline MMSE score, ADA, and NAb status at subject level were not significant predictors of ARIA-E. ApoE4 carrier status was the only statistically significant predictor in the model, where the incidence of ARIA-E in ApoE4 carriers is predicted to be approximately 2.6 times higher than in ApoE4 noncarriers. The predicted ARIA-E rate for ApoE4 carriers and ApoE4 noncarriers at mean Css,max (305 µg/mL) after lecanemab 10 mg/kg bi-weekly doses is 14.0% and 5.4%, respectively.

Figure 13: Observed and Model-Predicted ARIA-E incidence vs Model-Predicted Lecanemab Css,max.

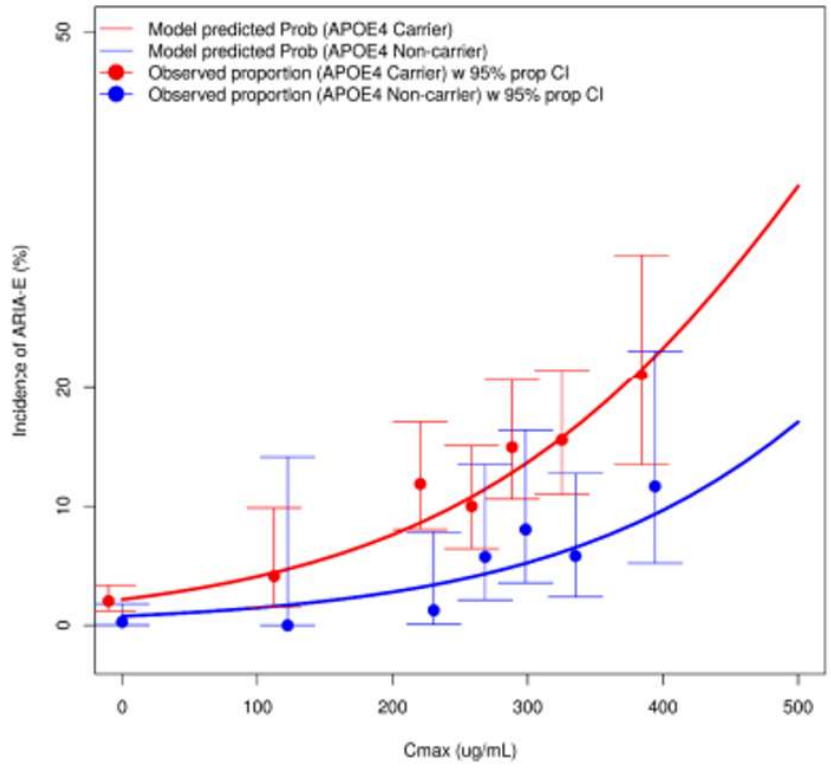
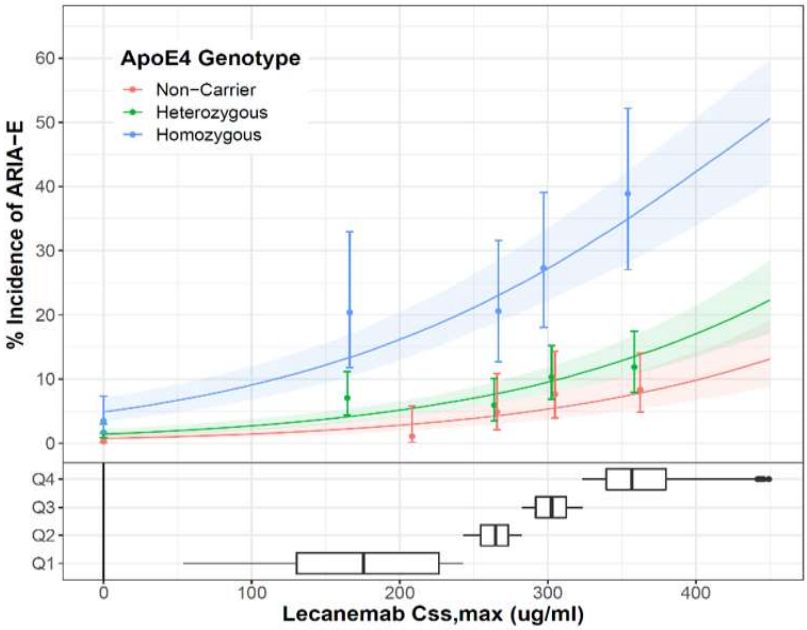


Figure 14: Observed and Model-Predicted ARIA-E Incidence vs Model-Predicted Lecanemab Css,max



In the top panel, filled circles represent pooled Study 201 Core and 301 Core observed incidence of ARIA-E for each lecanemab Css,max quartile (1Q-4Q) and placebo, plotted at the median Css,max of each group. Whiskers represent 95% confidence interval of the observed ARIA-E incidence. Solid simulated lines represent the model-predicted % incidence of ARIA-E in ApoE4 genotypes. The shaded areas represent the 95% confidence interval of the predicted incidence. In the bottom pane, the range of model-predicted Css,max values for the total Study 201 Core and 301 Core analysis set in each quartile is displayed.

ARIA-H can occur concurrently with ARIA-E or as isolated ARIA-H without ARIA-E. In Study 301 Core isolated ARIA-H events occurred throughout the course of treatment, while ARIA-H concurrent with ARIA-E tended to occur early in treatment. A total of 150 subjects from Study 301 Core experienced isolated ARIA-H, which is defined as ARIA-H without concurrent ARIA-E events. Table 8 shows the number of observed cases of isolated ARIA-H in Study 301 Core.

Table 8. Incidence of isolated ARIA-H in Study 301 Core

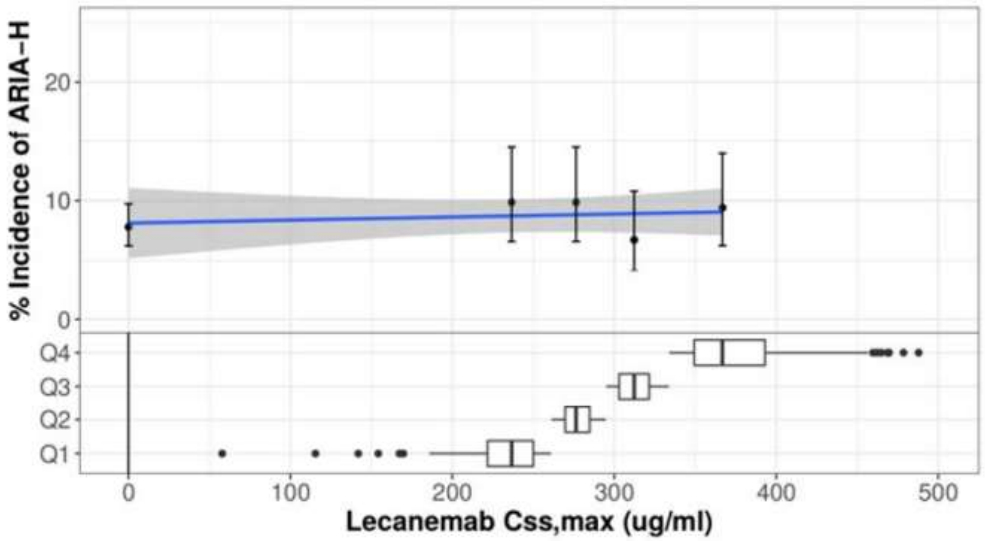
	Subjects Experiencing Isolated ARIA-H		
Treatment	One or More Cases	No Cases	Overall Incidence (%)
Placebo	70	827	7.80
LEC10-BW	80	812	8.99

ARIA-H = amyloid-related imaging abnormalities-hemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly

Graphical analysis showed that the incidence rate of isolated ARIA-H was independent of lecanemab exposure and was balanced between placebo and lecanemab-treated subjects. The incidence of isolated ARIA-H had no apparent correlation with lecanemab treatment or lecanemab exposure at lecanemab 10 mg/kg bi-weekly across ApoE4 genotypes.

The incidence rate of isolated ARIA-H appeared to be lower in heterozygous ApoE4 carriers and ApoE4 noncarriers compared to homozygous ApoE4 carriers.

Figure 15: Isolated ARIA-H Incidence in Study 301 Core as a Function of Model-Predicted Lecanemab Css,max



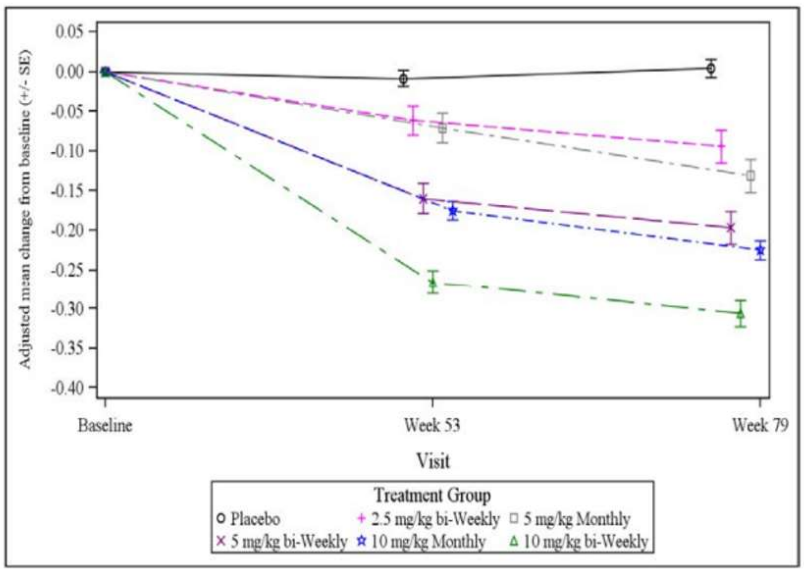
Dose Selection and Rationale

The lecanemab 10 mg/kg biweekly dosing regimen chosen for Study 301 was based on the large dose-range finding Study 201, which suggested that this dosing regimen most effectively removed brain amyloid load (as determined by amyloid PET) with a safety profile that was deemed to be acceptable, especially with regards to infusion reactions and ARIA-E. The results from Study 201 and 301 are presented below.

Maximum Brain Amyloid Reduction Achieved with lecanemab 10 mg/kg biweekly

Lecanemab demonstrated dose-dependent, time-dependent, and statistically significant brain amyloid reductions across all doses versus placebo. The greatest reduction was observed in the lecanemab 10 mg/kg biweekly dose. A least square mean change from baseline in brain amyloid levels as measured by amyloid PET SUVr reduction of 0.306 (LEC10-BW) and 0.225 (LEC10-M) was observed after 18 months of treatment (Figure 16).

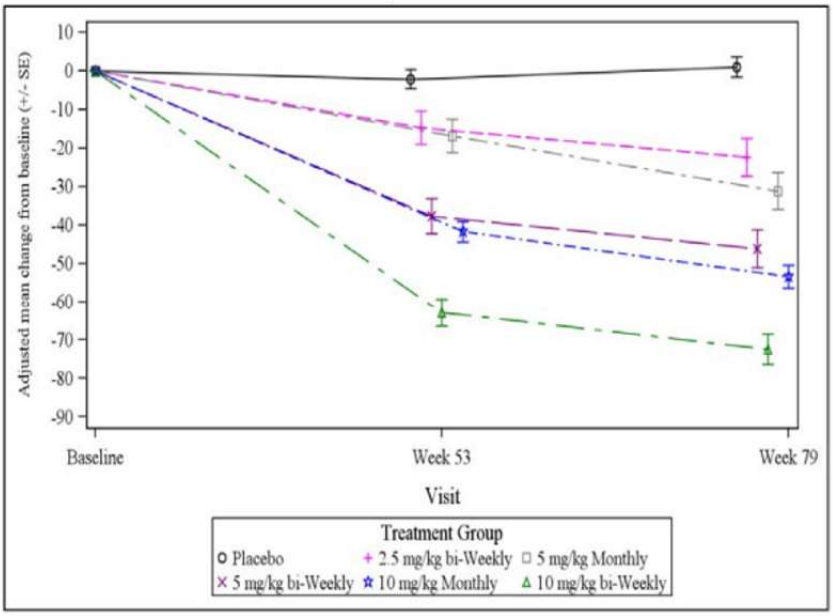
Figure 16: Least Square Mean Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET SUVr Normalised to whole cerebellum mask by Visit- Study 201 Core.



The PET SUVr results using the whole cerebellum (WC) reference region were also recalculated to the Centiloid scale. The results are presented with the Centiloid scale to help compare brain amyloid reduction results between different tracers.

Similar time-dependent amyloid CL with lecanemab 10 mg/kg biweekly was observed in Study 201 OLE Phase, with amyloid CL also observed at earlier timepoints (3 and 6 months). Additionally, lecanemab 10 mg/kg biweekly showed a statistically significant increase in CSF Aβ[1-42] in Study 201 Core, at 12 and 18 months. Statistically significant changes in plasma Aβ42/40 ratio and plasma p-tau181 were also seen in subjects treated with lecanemab 10 mg/kg biweekly.

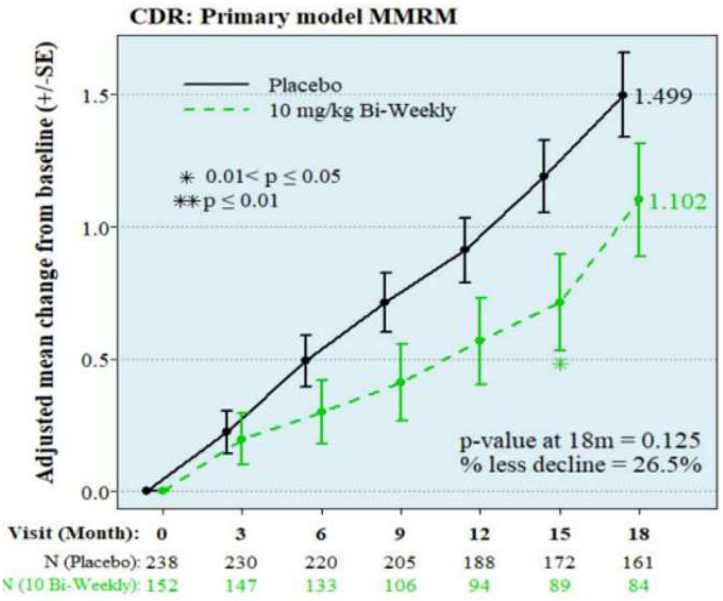
Figure 17: Least Square Mean (± SE) Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET in Centiloid Scales by Visit – Study 201 Core (PD Analysis Set)



Lecanemab demonstrated a dose dependent slowing of decline on CDR-SB over time, starting at 6 months of treatment. Lecanemab 10 mg/kg biweekly showed a slower decline (>25%) versus placebo across all time points. After 18 months of treatment, LEC10-BW showed a 26.5% slower clinical decline versus placebo (P = 0.125) (Figure 19).

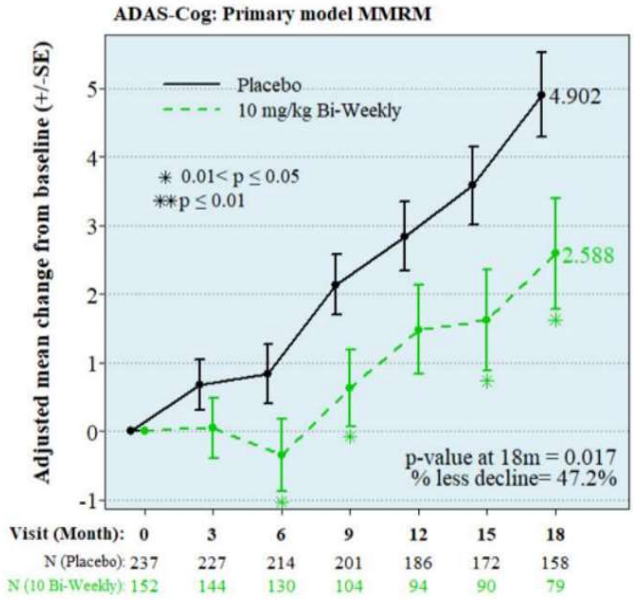
Including baseline by visit interaction in the primary model for CDR-SB improved the results (31% less decline on LEC10-BW with P value=0.062).

Figure 18: CDR-SB Change from Baseline lecanemab 10 mg/kg biweekly VS Placebo- Study 201 core



Lecanemab demonstrated a dose-dependent slowing of decline on ADAS-Cog14 over time compared to placebo. There was a slower decline on ADAS-Cog14 for LEC10-BW dose versus placebo across all time points. At 18 months, lecanemab 10 mg/kg biweekly showed a 47.2% slowing of clinical decline versus placebo (P=0.017).

Figure 19: ADAS-Cog14 Change from Baseline LEC10-BW VS Placebo- Study 201 core



PK/PD modelling predicted an exposure-dependent slowing of decline on CDR-SB and ADAS-Cog14 over time. Across tested doses, lecanemab10 mg/kg biweekly resulted in the highest exposures and showed greatest slowing in cognitive decline on CDR-SB and ADAS-Cog14. In addition, the PK/PD modelling showed that lecanemab 10 mg/kg biweekly resulted in a larger and faster decrease in PET Centiloid with time, regardless of ApoE4 status. The levels in plasma p-tau181 and plasma Aβ42/40 ratio, which are considered earlier and more sensitive indicators of brain amyloid accumulation, were significantly dependent on lecanemab exposure. The magnitude of change toward healthy levels for both biomarkers

was the highest for lecanemab 10 mg/kg biweekly.

Lecanemab 10 mg/kg biweekly was generally well-tolerated with similar incidence rates of treatment-emergent (TEAEs) and treatment-emergent serious adverse events (TESAEs) between placebo and lecanemab. Infusion-related reactions were the most common TEAE for lecanemab 10 mg/kg biweekly. The lower grades of infusion-related reaction severity, low rates of discontinuation due to infusion-related reactions, and response to preventative medication indicates that infusion-related reactions are readily manageable.

In Study 301 Core, 12.6% lecanemab 10 mg/kg biweekly subjects had ARIA-E and less than 3% were symptomatic. Most cases of ARIA-E occurred within the first 3 months of treatment, were dose-dependent, and typically resolved radiographically within 4 to 16 weeks. There were no dose response trends in the TEAE of isolated ARIA-H.

Rates of TEAEs across subgroups were consistent with the overall population, except for the incidence of ARIA-E which was higher in ApoE4 carriers, in particular homozygous ApoE4 carriers.

Immunogenicity
The extent of lecanemab-mediated brain amyloid clearance and the conversion to amyloid negativity was not affected by the presence of ADA. This result was further supported by PK/PD modelling where ADA status and NAb status at subject level did not impact drug effect on PET using Centiloids, plasma Aβ42/40 ratio, and p-tau181.

The slowing of cognitive decline (CDR SB and ADAS Cog14) with lecanemab 10 mg/kg biweekly relative to placebo is not affected by the presence of ADA and NAb.

Overall conclusion on pharmacodynamics and PK/PD
Lecanemab distinguishes itself from other anti-amyloid mAbs, in that it selectively targets large soluble protofibrils relative to monomers, with preferential activity over insoluble fibrils. Results of the *in vitro* ELISA studies showed that lecanemab selectively binds to Aβ protofibrils. Results with monomeric Aβ(1-40), small and large Aβ(1-42) protofibrils, showed binding affinities of small and large protofibrils to lecanemab (IC50 values: 0.80 and 0.79 nmol/L, respectively). Statistically significant reductions of Aβ-positive plaques were also seen in mouse studies.

Concurrent use of symptomatic treatments for AD (e.g. donepezil, rivastigmine, galantamine, tacrine, and memantine) showed that the TEAEs in subjects receiving lecanemab 10 mg/kg biweekly and those on a placebo were similar, irrespective of whether they were concurrently using approved AD treatment. The simultaneous utilisation of approved symptomatic AD treatment did not seem to influence the frequency of ARIA-E. The analysis of events of ARIA, ARIA-E and each subset of ARIA-H according to use of antiplatelet or anticoagulant therapy did not show an increase the risk of events of ARIA-E, ARIA-H microhaemorrhage or ARIA-H superficial siderosis, however, the numbers in the ARIA-H macrohaemorrhage subgroup, and the number of subjects that received combined therapy are too low to draw conclusions. At present it is considered that the risk of intracerebral haemorrhage with lecanemab treatment in patients treated with concomitant antithrombotic medication, particularly anticoagulants or a thrombolytic agent is not well characterised, and an increased risk cannot be excluded.

The effect of lecanemab to reduce brain amyloid was measured using biomarkers measured

by amyloid positron emission tomography (PET) imaging and changes in Aβ levels in plasma, and evidence of drug-related effect on downstream AD pathophysiology was further explored using p-tau181 in PKPD models.

A model was developed to describe the relationship between drug concentration and amyloid PET signal. The signal was predicted to decline more quickly in subjects with higher lecanemab exposure. Age also has an effect on the rate of amyloid CL. A typical 83-year-old subject is predicted to achieve amyloid negativity (<30 Centiloids) by approximately 32 weeks of treatment, a typical younger 57-year-old subjects would require longer than 18 months of treatment to achieve amyloid negativity. ApoE4 carrier status had an effect on baseline amyloid, the higher baseline level of amyloid resulted in a faster initial rate of removal in ApoE4 carriers; however, at the end of the 18-month treatment period, amyloid levels were similar. The t½ of amyloid re-accumulation is estimated to be approximately 14 years.

Models were also developed to describe the relationship between drug concentration and plasma Aβ42/40 and P-tau181. The effects appear relatively small over placebo, particularly in study 201. In addition, the time to re-accumulation in plasma was much shorter than for brain.

Plasma Aβ42/40 ratio was predicted to increase more quickly in subjects with higher lecanemab exposure. Plasma p-tau181 is also expected to decrease more quickly in subjects with higher lecanemab exposure.

With respect to the clinical relevance of the changes in plasma biomarkers, Aβ42/40 ratio and p-tau181 levels are known to be altered in Alzheimer's disease patients. Plasma Aβ42/40 has been shown to predict amyloid PET levels, with lower ratios
associated with greater amyloid PET signal. Accordingly, the increase in Aβ42/40 ratio associated with lecanemab administration can reasonably be thought to reflect lecanemab efficacy through reduced brain amyloid. Increases in plasma p-tau181 have been associated with AD and amyloid plaques, neuritic dystrophy, and neurofibrillary tangles.

It can be agreed that in plasma, p-tau181 could be reasonably assumed to reflect a reduction in brain amyloid and associated neuritic dystrophy and tau deposition, however the lack of understanding of PKPD currently limits its usefulness as a biomarker.

For each clinical endpoint, CDR-SB and ADAS-Cog14, a PK/PD model was developed introducing lecanemab exposure effect on the progression rate as a linear function. Css,av was selected as the exposure parameter for both CDR-SB and ADAS-Cog14 models. Significant covariates identified in the final PK/PD model for CDR-SB indicated that: Asian subjects had 10% lower baseline CDR-SB than other subjects. Mild AD subjects had 53% higher baseline CDR-SB and 50% faster disease progression rate than MCI subjects. Subjects with AD symptomatic medication at baseline had 67% faster disease progression rate than subjects without AD symptomatic medication. ApoE4 carrier status did not significantly affect the disease progression rate but there are limitations around the data. Median lecanemab Css,av in subjects who received lecanemab 10 mg/kg biweekly in Study 301 Core was 153 µg/mL, the associated model-predicted decline in disease progression was 34.2% (95% CI: 31.8% – 36.5%).

Significant covariates identified in the final PK/PD model for ADAS-Cog14 indicated that: Asian subjects had 13% higher baseline ADAS-Cog14 than other subjects. Baseline ADAS-

Cog14 score increased with age. Mild AD subjects had 19% higher baseline ADAS-Cog14 and 58% faster disease progression rate than MCI subjects. Subjects with AD symptomatic medication at baseline had 11% higher baseline ADAS-Cog14 and 79% faster disease progression rate than subjects without AD symptomatic medication at baseline. There were no significant effects of age, sex, weight, race/ethnicity, and ApoE4 carrier status on disease progression rate. The model predicted an exposure-dependent slowing of cognition decline on ADAS-Cog14. For median lecanemab Css,av in subjects who received LEC10-BW in Study 301 (153 μg/mL), the associated model-predicted decline in disease progression was 31.0% (95% CI: 25.2 – 36.8%) for ADAS-Cog14.

A logit model describing the incidence of ARIA-E as a function of lecanemab exposure was developed, Css,max was selected as the best predictor of incidence of ARIA-E and showed a clear exposure response relationship. Age, body weight, race/ethnicity, sex, baseline MMSE score, ADA, and NAb status at subject level were not significant predictors of ARIA-E. ApoE4 carrier status was the only statistically significant predictor in the model, where the incidence of ARIA-E in ApoE4 carriers is predicted to be approximately 2.6 times higher than in ApoE4 noncarriers. The predicted ARIA-E rate for ApoE4 carriers and ApoE4 noncarriers at mean Css,max (305 μg/mL) after lecanemab 10 mg/kg bi-weekly doses is 14.0% and 5.4%, respectively.

Graphical analysis showed that the incidence rate of isolated ARIA-H was independent of lecanemab exposure and was balanced between placebo and lecanemab-treated subjects. The incidence of isolated ARIA-H had no apparent correlation with lecanemab treatment or lecanemab exposure at LEC10-BW across ApoE4 genotypes.

The dose was selected based on the phase 2 study. Lecanemab 10 mg/kg biweekly resulted in the highest exposures and showed greatest slowing in cognitive decline on CDR-SB and ADAS-Cog14. In addition, the PK/PD modelling showed that lecanemab 10 mg/kg biweekly resulted in a larger and faster decrease in PET Centiloid with time, regardless of ApoE4 status. The levels in plasma p-tau181 and plasma Aβ42/40 ratio, which are considered earlier and more sensitive indicators of brain amyloid accumulation, were dependent on lecanemab exposure and was highest for the lecanemab 10 mg/kg biweekly dose. Initiating lecanemab treatment at 10 mg/kg biweekly, the target clinical dose, is suggested to allow for quick achievement of therapeutically relevant steady-state PK and rapid brain amyloid removal with an acceptable safety profile.

IV.4 Clinical efficacy

The single pivotal study 301 Core is the primary data set supporting the efficacy of lecanemab (also referred to as BAN2401) in early Alzheimer's disease (AD). Supportive data is provided from study 201 Core and the open label extension phases of study 201 and 301.

Study BAN2401-G000-201 (201) – Dose Response Study

This was a Placebo-Controlled, Double–Blind, Parallel-Group, Bayesian Adaptive Randomisation Design and Dose Regimen–Finding Study, with an Open-Label Extension Phase, to Evaluate Safety, Tolerability and Efficacy of BAN2401 in Subjects with Early Alzheimer's Disease.

Methods

Study 201 is a global, multicentre study using a Bayesian design with response-adaptive randomisation (RAR) to evaluate safety, tolerability, and efficacy of lecanemab. The study incorporated multiple blinded interim analyses to allow for RAR of subjects across placebo

or 5 active arms of lecanemab to determine the most efficacious dose regimen on the Alzheimer's Disease Composite Score (ADCOMS) at 12 months of treatment. Study 201 Core had an 18-month treatment period followed by a 3-month follow-up period. All subjects were required to complete 18 months of study irrespective of results of the 12-month interim analysis.

There were 2 optional substudies in Study 201 Core: amyloid PET substudy and CSF substudy. Subjects who consented to the amyloid PET substudy had PET scans performed at Baseline, 12, and 18 months. Subjects who consented to CSF substudy had CSF samples collected at these same timepoints.

Health authority recommendations for LEC10-BW dose group

During the study, emerging data indicated that homozygous apolipoprotein ϵ4 variant (ApoE4) carriers on the highest dose of lecanemab (10 mg/kg biweekly) had the highest risk of developing symptomatic amyloid–related imaging abnormalities with cerebral edema (ARIA–E). Thus, the independent Data Safety Monitoring Board (DSMB) recommended not to randomise homozygous ApoE4 carriers to the 10 mg/kg biweekly (LEC10-BW) dose and the study design was amended to add a Week 9 safety MRI scan enabling earlier detection of ARIA-E. Following this DSMB recommendation, Health Authorities in the EU requested that the applicant stop the randomisation of ApoE4 carriers (heterozygous or homozygous) to the LEC10-BW dose and that ApoE4 carriers who had been on the LEC10-BW dose for less than 6 months were to be immediately discontinued (resulting in 25 of the 337 subjects discontinuing study treatment). A Week 7 safety MRI was also implemented in the EU only. Subjects who continued the study remained on that same dose throughout treatment.

Study participants

Diagnosis

- Mild cognitive impairment (MCI) due to AD – intermediate likelihood, defined as: meeting National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD – intermediate likelihood; a Clinical Dementia Rating (CDR) score of 0.5 and a Memory Box score of 0.5 or greater at Screening and Baseline; and a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; or
- Mild AD dementia, defined as meeting the NIA-AA core clinical criteria for probable AD dementia; and a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater at Screening and Baseline.

Key inclusion criteria

- Men and women aged between 50 and 90 years, inclusive, with objective impairment in episodic memory as indicated by at least 1 SD below age-adjusted mean in the Wechsler Memory Scale-IV Logical Memory (subscale) II (WMS-IV LM II).
- Positive amyloid load as indicated by 1 of the following:
  a. PET assessment of imaging agent uptake into brain.
  b. CSF assessment of Aβ(1-42).
- MMSE score equal to or greater than 22, and equal to or less than 30 at Screening and Baseline, except in France, Germany, Netherlands, Spain, Sweden, and United Kingdom, where the MMSE score was equal to or greater than 22 and equal to or less than 28 at Screening and Baseline.
- Subjects receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD dementia had to be on a stable dose for at least 12 weeks prior to Baseline. Treatment-naïve early AD subjects could be included in the study. Use of memantine

was not allowed for Japanese subjects.

Main exclusion criteria
Subjects were excluded from the study if they had any neurological condition that could have contributed to cognitive impairment above and beyond that caused by the subject's AD; any psychiatric diagnosis or symptoms that could have interfered with study procedures in the subject; Geriatric Depression Scale score greater or equal to 8 at screening; evidence of other clinically significant lesions that could indicate a dementia diagnosis resulting from anything other than AD on brain MRI at Screening; and other significant pathological findings on brain MRI at Screening, including but not limited to: more than 4 microhaemorrhages (≤10 mm at the greatest diameter), a single microhaemorrhage >10 mm at greatest diameter, an area of superficial siderosis, evidence of vasogenic oedema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, infective lesions, evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease or space occupying lesions or brain tumours.

Anticoagulants (e.g., warfarin, dabigatran) were not permitted for 7 days or 5 half-lives, whichever was longer, before Baseline until the Follow-Up Visit. Subjects required to start chronic (>4 weeks) anticoagulant treatment during the study were withdrawn from study drug. Short-term (<4 weeks) treatment with anticoagulants was permitted - study drug was temporarily suspended during this anticoagulant therapy.

Treatments
Study 201 Core evaluated doses of lecanemab 2.5 mg/kg biweekly (LEC2.5-BW) to LEC10-BW based on the integrated review of the safety and PK information collected in Study 101 and nonclinical PK/PD modelling of soluble Aβ aggregate brain reduction in mice (Table CE 1).

Table CE1: Study treatments administered

BAN2401 Dose (mg/kg)	Infusion Frequency
Placebo	2-week intervals
2.5	2-week intervals
5.0	4-week intervals[a]
5.0	2-week intervals
10.0	4-week intervals[a]
10.0[b]	2-week intervals

a: Subjects who received study drug at 4-week intervals (monthly) received placebo at the intervening 2-week time points.
b: Subjects confirmed as ApoE4 carriers (homozygous or heterozygous) were not randomized to the 10 mg/kg 2-week interval (biweekly) dose after Protocol Amendments 04 and 05

Study drug doses were not reduced during the study. If a subject was unable to tolerate the assigned study treatment, it was discontinued, and no further infusions administered.

Study drug was discontinued in all patients with ARIA-E and in patients who developed any macrohaemorrhages greater than 10 mm, an area of superficial siderosis, or symptomatic treatment-emergent microhaemorrhages. There were no dose reductions and no resumption of dosing after resolution of ARIA-E or ARIA-H. Administration of study drug was also to be terminated for infusion reactions of Grade 3 severity or above, clinical features indicating meningoencephalitis, or hypersensitivity reactions with clinical features of tissue injury.

Objectives and endpoints

Primary efficacy objective

- To evaluate the efficacy of lecanemab compared to placebo by establishing the dose regimen with at least 90% of the maximum effective dose (dmax) treatment effect (ED90) for BAN2401 on ADCOMS at 12 months of treatment in subjects with Early Alzheimer's Disease (EAD), defined as MCI due to AD – intermediate likelihood or mild AD dementia.

Primary efficacy endpoint

- Change from Baseline in ADCOMS at 12 months.

Key secondary efficacy endpoints

- Change from Baseline at 18 months in brain amyloid pathophysiology as measured by amyloid PET.
- Change from Baseline in ADCOMS at 18 months.
- Change from Baseline in CDR-SB at 18 months.
- Change from Baseline in ADAS–Cog14 at 18 months.
- Change from Baseline in CSF biomarkers (including Aβ[1-42], t-tau, and p-tau) at 18 months.
- Change from Baseline in total hippocampal volume at 18 months using volumetric MRI (vMRI)

ADCOMS

The Alzheimer's Disease Composite Score is a weighted linear combination of items from 3 commonly used scales: 4 items from the ADAS-Cog (delayed word recall, orientation, word recognition, and word finding), two items from the Mini-Mental State Examination (orientation to time and drawing), and all 6 items from the CDR-SB. This endpoint was designed by Eisai to enhance the early allocation of subjects in the Bayesian design in Study 201 (and was included in Study 301 to demonstrate reproducibility of results). The maximum composite score is 1.97. The range of this new composite score is therefore between 0 and 1.97 with higher scores indicating greater impairment.

Amyloid PET

Amyloid plaque load identified by 18F-florbetapir PET imaging uptake was determined via 2 separate methodologies: visual read and standard uptake value ratio (SUVr) versus a reference region. The primary amyloid PET analysis was the SUVR calculated for a composite cortical region of interest with whole cerebellum mask as a reference region. Different reference regions were also assessed and used for sensitivity analyses.

CDR-SB

The Clinical Dementia Rating – Sum of Boxes is based on patient and caregiver interview assessing 3 domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care). Each domain is scored 0 (unimpaired), 0.5 (MCI), 1 (mild), 2 (moderate), 3 (severe). Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating greater disease severity.

ADAS-Cog14

The Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks is the most widely used cognitive scale in AD studies. It is a cognitive test administered to the patient assessing domains of memory, orientation, language and praxis (performing skilled or

learned motor movements). The modified version used in this study is scored from 0 to 90 points with a score of 0 indicating no impairment, and a score of 90 indicating maximum impairment.

Statistics

Randomisation

A dose-finding response-adaptive randomisation (RAR) was carried out. This meant that after an initial period of randomisation (the 'burn-in period'), data from interim analyses were used to update subsequent randomisation probabilities to favour allocation to the most promising dosing regimen. The randomisation probability for the most promising dosing regimen was mirrored for the placebo group but decreased for other doses.

The burn-in period included 196 patients who were randomised to placebo versus any of the 5 active treatment arms in a 4:2:2:2:2:2 ratio. Interim analyses to update randomisation probabilities took place after randomisation of 196 patients and approximately every 50 patients thereafter up to a maximum of 800 patients.

Following Amendment 5 of the protocol, subjects who were ApoE4 carriers were no longer randomised to the 10 mg/kg biweekly dose or were discontinued from the study if on this dose for ≤6 months.

Primary efficacy analyses

The primary endpoint was analysed using pre-specified Bayesian methods among randomised subjects who received at least 1 dose of study drug, had a baseline assessment, and had at least 1 post-dose efficacy assessment. The primary endpoint was analysed regardless of initiation of new AChEIs or memantine, or dose adjustment of stable AChEIs or memantine.

Trial success was defined by the probability of obtaining a 25% improvement in ADCOMS for ED_{90} compared with placebo. The threshold for success was a probability >95% in any interim analysis or a probability of ≥80% in the primary analysis at 12 months.

Bayesian simulations estimated that there was a 10% probability of observing trial success when there was no true treatment effect (the "null" scenario). This was the 1-sided Type I error rate of this trial assuming a 20% dropout rate at 12 months. Increasing the dropout rate to 30% or 40% resulted in a corresponding simulated type I error of 10.6% or 12.5%, respectively.

Statistical tests for conventional analyses were based on a two-sided 10% or one-sided 5% level of significance.

Interim analyses

Success and futility of the trial were assessed using Bayesian methods at each interim analysis up to and including the enrolment of the 800th patient and every 3 months thereafter until the primary analysis at 12 months of treatment. There was no formal type I error control for interim analyses.

Summary of the design and conduct of study 201 core

Overall, the design and conduct of study 201 core is acceptable for a dose-finding study. However, due to methodological issues, the results are considered exploratory only. In particular: the lack of control of the alpha risk (including that analyses have not been adjusted

for multiple comparisons), the use of a Bayesian response adaptive randomisation, and the change in randomisation strategy implemented whilst the study was ongoing to exclude ApoE4 carriers from the highest dose of 10 mg/kg biweekly in response to emerging safety data. In addition, the primary efficacy endpoint 'Change from baseline in ADCOMS at 12 months' is not fully validated, and it differs to that used in the pivotal clinical trial and was evaluated at a different time point (12m vs 18 months in study 301).

Results (Core)

A total of 856 subjects were randomised to receive either placebo (247 subjects) or lecanemab (609 subjects). Except for 2 subjects in the placebo group, all subjects received at least one dose of study drug. In-keeping with the response-adaptive randomisation, the number of subjects varied across the 5 lecanemab treatment groups with the highest number of subjects randomised to the 10mg/kg monthly (253) and 10mg/kg biweekly (161) groups.

A higher percentage of subjects in the lecanemab group (38.4%) discontinued the study compared to placebo (27.8%). This higher percentage of discontinuation was primarily driven by the rates in the lecanemab 10mg/kg monthly (38.7%) and 10mg/kg biweekly (46.0%) dose groups and related to events of ARIA-E (all ARIA-E cases resulted in immediate discontinuation per protocol) or as a consequence of the protocol amendment required by Health Authorities in the EU which required discontinuation of ApoE4 carriers on the 10mg/kg biweekly dose for less than 6 months.

Table CE2: Subject Disposition and Reasons for Discontinuation from the Study – Study 201 Core (All Randomised Subjects)

		Lecanemab					
	PBO	2.5 mg/kg Biweekly	5 mg/kg Monthly	5 mg/kg Biweekly	10 mg/kg Monthly	10 mg/kg Biweekly	Total
Randomized, n	247	52	51	92	253	161	609
Not treated, n	2	0	0	0	0	0	0
Treated, n	245	52	51	92	253	161	609
Completed the study, n (%)[a]	177 (72.2)	35 (67.3)	37 (72.5)	61 (66.3)	155 (61.3)	87 (54.0)	375 (61.6)
Discontinued from the study, n (%)[a]	68 (27.8)	17 (32.7)	14 (27.5)	31 (33.7)	98 (38.7)	74 (46.0)	234 (38.4)
Primary reason for discontinuation[b]							
Adverse event[c]	10 (4.1)	4 (7.7)	2 (3.9)	5 (5.4)	23 (9.1)	12 (7.5)	46 (7.6)
Lost to follow-up	7 (2.9)	0	1 (2.0)	2 (2.2)	4 (1.6)	3 (1.9)	10 (1.6)
Subject choice	15 (6.1)	5 (9.6)	2 (3.9)	7 (7.6)	14 (5.5)	8 (5.0)	36 (5.9)
Withdrawal of consent	23 (9.4)	1 (1.9)	5 (9.8)	13 (14.1)	37 (14.6)	20 (12.4)	76 (12.5)
Other	13 (5.3)	7 (13.5)	4 (7.8)	4 (4.3)	20 (7.9)	31 (19.3)	66 (10.8)

Baseline data

In the full analysis set (FAS), overall, most subjects were white, the median age was 72 and there were similar percentages of males and females. Overall, 64.1% of subjects had a diagnosis of MCI due to AD and 35.9% had mild AD, consistent with the study design. The median time since diagnosis was 2 years and just over half of subjects were taking concomitant approved symptomatic AD treatment at baseline.

Most subjects were ApoE4 carriers (71.4%); 54.9% heterozygous and 16.5% homozygous, with similar percentages of carriers in the placebo group and when combining the lecanemab groups. However, the ApoE4 status was imbalanced across lecanemab treatment groups because of the protocol amendments required whereby ApoE4 carriers could no longer be randomised to the 10mg/kg biweekly dose. Therefore, there were far fewer ApoE4 carriers in this group (30.3%) with the RAR allocating most of the ApoE4 carriers to the next most efficacious groups, potentially impacting the interpretation of the study results.

The baseline values for clinical outcome scores were similar across treatment groups.

Table CE3: Demographic and Baseline Characteristics – Study 201 Core (Full Analysis Set)

Category		PBO (N=238)	Lecanemab 2.5 mg/kg Biweekly (N=52)	Lecanemab 5 mg/kg Monthly (N=48)	Lecanemab 5 mg/kg Biweekly (N=89)	Lecanemab 10 mg/kg Monthly (N=246)	Lecanemab 10 mg/kg Biweekly (N=152)	Lecanemab Total (N=587)	Combined Total (N=825)
Age (year)[a]	n	238	52	48	89	246	152	587	825
	Mean (SD)	71.11 (8.892)	70.50 (8.257)	70.42 (7.514)	70.64 (7.446)	71.26 (7.455)	72.64 (8.777)	71.39 (7.907)	71.31 (8.198)
	Median	72.00	70.50	71.00	72.00	71.00	73.00	72.00	72.00
	Min, max	50.0, 89.0	50.0, 86.0	55.0, 84.0	52.0, 87.0	53.0, 90.0	51.0, 88.0	50.0, 90.0	50.0, 90.0
Age group, n (%)	<65 years	55 (23.1)	11 (21.2)	9 (18.8)	20 (22.5)	44 (17.9)	27 (17.8)	111 (18.9)	166 (20.1)
	≥65 to <80 years	144 (60.5)	35 (67.3)	35 (72.9)	60 (67.4)	168 (68.3)	94 (61.8)	392 (66.8)	536 (65.0)
	≥80 years	39 (16.4)	6 (11.5)	4 (8.3)	9 (10.1)	34 (13.8)	31 (20.4)	84 (14.3)	123 (14.9)
Sex, n (%)	Male	101 (42.4)	26 (50.0)	24 (50.0)	41 (46.1)	136 (55.3)	88 (57.9)	315 (53.7)	416 (50.4)
	Female	137 (57.6)	26 (50.0)	24 (50.0)	48 (53.9)	110 (44.7)	64 (42.1)	272 (46.3)	409 (49.6)
Ethnicity, n (%)	Hispanic or Latino	9 (3.8)	4 (7.7)	1 (2.1)	3 (3.4)	9 (3.7)	9 (5.9)	26 (4.4)	35 (4.2)
	Not Hispanic or Latino	229 (96.2)	48 (92.3)	47 (97.9)	86 (96.6)	237 (96.3)	143 (94.1)	561 (95.6)	790 (95.8)
Race, n (%)	White	216 (90.8)	48 (92.3)	46 (95.8)	7 (82.0)	222 (90.2)	141 (92.8)	530 (90.3)	746 (90.4)
	Black or African American	5 (2.1)	2 (3.8)	1 (2.1)	4 (4.5)	4 (1.6)	4 (2.6)	15 (2.6)	20 (2.4)
	Asian	16 (6.7)	2 (3.8)	1 (2.1)	9 (10.1)	17 (6.9)	7 (4.6)	36 (6.1)	52 (6.3)
	Chinese	1 (<1.0)	0	0	0	0	0	0	1 (<1.0)
	Japanese	10 (4.2)	1 (1.9)	0	6 (6.7)	12 (4.9)	5 (3.3)	24 (4.1)	34 (4.1)
	Other Asian	5 (2.1)	1 (1.9)	1 (2.1)	3 (3.4)	5 (2.0)	2 (1.3)	12 (2.0)	17 (2.1)
	Other	1 (<1.0)	0	0	3 (3.4)	3 (1.2)	0	6 (1.0)	7 (<1.0)
Region, n (%)	North America	195 (81.9)	47 (90.4)	41 (85.4)	70 (78.7)	215 (87.4)	135 (88.8)	508 (86.5)	703 (85.2)
	Western Europe	28 (11.8)	4 (7.7)	6 (12.5)	7 (7.9)	15 (6.1)	10 (6.6)	42 (7.2)	70 (8.5)
	Asia	15 (6.3)	1 (1.9)	1 (2.1)	12 (13.5)	16 (6.5)	7 (4.6)	37 (6.3)	52 (6.3)
APOE4 status, n (%)	Carrier	169 (71.0)	38 (73.1)	37 (77.1)	81 (91.0)	218 (88.6)	46 (30.3)	420 (71.6)	589 (71.4)
	Heterozygous	129 (54.2)	33 (63.5)	26 (54.2)	67 (75.3)	160 (65.0)	38 (25.0)	324 (55.2)	453 (54.9)
	Homozygous	40 (16.8)	5 (9.6)	11 (22.9)	14 (15.7)	58 (23.6)	8 (5.3)	96 (16.4)	136 (16.5)
	Noncarrier	69 (29.0)	14 (26.9)	11 (22.9)	8 (9.0)	28 (11.4)	106 (69.7)	167 (28.4)	236 (28.6)
Disease stage, n (%)	MCI due to AD	154 (64.7)	34 (65.4)	33 (68.8)	52 (58.4)	166 (67.5)	90 (59.2)	375 (63.9)	529 (64.1)
	Mild AD	84 (35.3)	18 (34.6)	15 (31.3)	37 (41.6)	80 (32.5)	62 (40.8)	212 (36.1)	296 (35.9)
AChEIs and/or	No	110 (46.2)	24 (46.2)	23 (47.9)	33 (37.1)	115 (46.7)	73 (48.0)	268 (45.7)	378 (45.8)
memantine at Baseline, n (%)	Yes	128 (53.8)	28 (53.8)	25 (52.1)	56 (62.9)	131 (53.3)	79 (52.0)	319 (54.3)	447 (54.2)
Number of years of disease since diagnosis	n	237	52	48	89	245	152	586	823
	Mean (SD)	2.38 (1.659)	2.27 (1.705)	2.08 (1.235)	2.16 (1.242)	2.20 (1.551)	2.22 (1.491)	2.19 (1.479)	2.25 (1.534)
	Median	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	Min, max	1.0, 11.0	1.0, 7.0	1.0, 6.0	1.0, 6.0	1.0, 12.0	1.0, 9.0	1.0, 12.0	1.0, 12.0
Age at diagnosis (years)	n	237	52	48	89	245	152	586	823
	Mean (SD)	70.32 (8.740)	69.75 (8.364)	69.94 (7.575)	70.09 (7.442)	70.71 (7.526)	72.03 (8.855)	70.81 (7.971)	70.67 (8.197)
	Median	70.00	70.00	71.00	71.00	71.00	73.00	71.00	71.00
	Min, max	50.0, 90.0	49.0, 86.0	54.0, 84.0	52.0, 87.0	52.0, 90.0	51.0, 89.0	49.0, 90.0	49.0, 90.0
Age at onset of symptoms (years)	n	238	52	48	89	246	152	587	825
	Mean (SD)	68.00 (8.880)	67.35 (8.220)	67.13 (7.601)	67.93 (7.513)	68.48 (7.815)	69.95 (9.057)	68.57 (8.156)	68.40 (8.370)
	Median	68.00	68.00	67.50	69.00	69.00	71.00	69.00	69.00
	Min, max	46.0, 88.0	47.0, 83.0	51.0, 82.0	50.0, 87.0	45.0, 89.0	47.0, 87.0	45.0, 89.0	45.0, 89.0

Table CE4: Baseline summary statistics of clinical efficacy endpoints overall – study 201 core (FAS)

Parameter		Placebo (N=238)	Lecanemab 2.5 mg/kg Biweekly (N=52)	Lecanemab 5 mg/kg Monthly (N=48)	Lecanemab 5 mg/kg Biweekly (N=89)	Lecanemab 10 mg/kg Monthly (N=246)	Lecanemab 10 mg/kg Biweekly (N=152)	Lecanemab Total (N=587)
CDR-SB	n	238	52	48	89	246	152	587
	Mean (SD)	2.89 (1.454)	2.98 (1.584)	2.94 (1.420)	3.03 (1.314)	2.91 (1.320)	2.97 (1.401)	2.95 (1.369)
	Median	3.00	3.00	2.50	3.00	2.50	3.00	3.00
	Min, max	0.50, 9.00	0.50, 7.00	1.00, 6.00	0.50, 6.50	0.50, 8.00	0.50, 8.50	0.50, 8.50
ADAS-Cog14	n	237	52	47	89	246	152	586
	Mean (SD)	22.56 (7.657)	22.72 (8.050)	22.94 (7.735)	22.75 (6.696)	21.90 (7.302)	22.06 (7.667)	22.23 (7.400)
	Median	22.00	22.50	22.33	23.67	21.33	22.67	22.00
	Min, max	6.00, 46.67	10.00, 42.33	8.67, 47.33	8.67, 39.00	3.67, 48.33	4.33, 42.00	3.67, 48.33
ADCOMS	n	238	52	48	89	246	152	587
	Mean (SD)	0.370 (0.1663)	0.386 (0.1970)	0.395 (0.1746)	0.390 (0.1558)	0.373 (0.1522)	0.373 (0.1508)	0.378 (0.1584)
	Median	0.36	0.38	0.36	0.39	0.36	0.37	0.37
	Min, max	0.05, 0.94	0.07, 0.87	0.10, 0.78	0.11, 0.78	0.06, 0.89	0.04, 0.87	0.04, 0.89
MMSE	n	238	52	48	89	246	152	587
	Mean (SD)	26.01 (2.348)	25.67 (2.487)	25.25 (2.622)	25.60 (2.260)	25.71 (2.364)	25.61 (2.351)	25.62 (2.373)
	Median	26.00	26.00	25.00	26.00	26.00	26.00	26.00
	Min, max	22.00, 30.00	22.00, 30.00	22.00, 30.00	22.00, 30.00	21.00, 30.00	22.00, 30.00	21.00, 30.00

Numbers analysed

Table CE5: Analysis sets – the randomised set

Analysis Sets	Placebo (N=247) n (%)	BAN2401 2.5 mg/kg Biweekly (N=52) n (%)	BAN2401 5 mg/kg Monthly (N=51) n (%)	BAN2401 5 mg/kg Biweekly (N=92) n (%)	BAN2401 10 mg/kg Monthly (N=253) n (%)	BAN2401 10 mg/kg Biweekly (N=161) n (%)	BAN2401 Total (N=609) n (%)	Combined Total (N=856) n (%)
Safety Analysis Set[a]	245 (99.2)	52 (100.0)	51 (100.0)	92 (100.0)	253 (100.0)	161 (100.0)	609 (100.0)	854 (99.8)
Full Analysis Set[b]	238 (96.4)	52 (100.0)	48 (94.1)	89 (96.7)	246 (97.2)	152 (94.4)	587 (96.4)	825 (96.4)
PP Analysis Set[c]	236 (95.5)	50 (96.2)	46 (90.2)	89 (96.7)	242 (95.7)	152 (94.4)	579 (95.1)	815 (95.2)
PK Analysis Set[d]	0	52 (100.0)	51 (100.0)	92 (100.0)	251 (99.2)	161 (100.0)	607 (99.7)	607 (70.9)
PD Analysis Set 1[e]	209 (84.6)	41 (78.8)	46 (90.2)	73 (79.3)	188 (74.3)	99 (61.5)	447 (73.4)	656 (76.6)
PD Analysis Set 2[f]	99 (40.1)	28 (53.8)	28 (54.9)	27 (29.3)	89 (35.2)	44 (27.3)	216 (35.5)	315 (36.8)
PD Analysis Set 3[g]	24 (9.7)	7 (13.5)	13 (25.5)	20 (21.7)	16 (6.3)	12 (7.5)	68 (11.2)	92 (10.7)

Percentages are based on the number of randomized subjects in the relevant treatment group.
CSF = cerebrospinal fluid, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, PP = Per Protocol, vMRI = volumetric magnetic resonance imaging.
a: The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
b: The Full Analysis Set is the group of randomized subjects who received at least 1 dose of study drug and had Baseline and at least 1 postdose primary efficacy measurement.
c: The PP Analysis Set is the subset of subjects in the Full Analysis Set who complied with the protocol.
d: The PK Analysis Set is the group of subjects with at least 1 quantifiable BAN2401 serum concentration with a documented dosing history.
e: The PD Analysis Set 1 is the group of subjects who had sufficient vMRI data to derive at least 1 vMRI parameter.
f: The PD Analysis Set 2 is the group of subjects who had sufficient amyloid PET data to derive at least 1 amyloid PET parameter.
g: The PD Analysis Set 3 is the group of subjects who had sufficient CSF data to derive at least 1 CSF parameter.

Outcomes and estimation

Primary Endpoint

- Change from Baseline in ADCOMS at 12 months.

The observed mean (SD) changes in ADCOMS from Baseline to 12 months are presented in the table below.

Table CE6: Summary statistics for change from baseline in ADCOMS at 12 months – FAS

Parameter Visit Statistic	Placebo (N=238)	BAN2401 2.5 mg/kg Biweekly (N=52)	BAN2401 5 mg/kg Monthly (N=48)	BAN2401 5 mg/kg Biweekly (N=89)	BAN2401 10 mg/kg Monthly (N=246)	BAN2401 10 mg/kg Biweekly (N=152)	BAN2401 Combined 10 mg/kg Monthly and Biweekly (N=398)
ADCOMS – Overall							
Baseline							
n	238	52	48	89	246	152	398
Mean (SD)	0.370 (0.1663)	0.386 (0.1970)	0.395 (0.1746)	0.390 (0.1558)	0.373 (0.1522)	0.373 (0.1508)	0.373 (0.1515)
Median	0.36	0.38	0.36	0.39	0.36	0.37	0.36
Min, max	0.05, 0.94	0.07, 0.87	0.10, 0.78	0.11, 0.78	0.06, 0.89	0.04, 0.87	0.04, 0.89
Week 53 (Month 12)							
n	206	42	45	69	181	98	279
Mean (SD)	0.460 (0.2454)	0.534 (0.2956)	0.492 (0.2538)	0.477 (0.2177)	0.444 (0.2215)	0.460 (0.2266)	0.450 (0.2230)
Median	0.42	0.46	0.48	0.45	0.41	0.42	0.41
Min, max	0.03, 1.50	0.03, 1.23	0.10, 1.49	0.07, 0.99	0.05, 1.26	0.07, 1.19	0.05, 1.26
Change from Baseline							
n	206	42	45	69	181	98	279
Mean (SD)	0.102 (0.1554)	0.149 (0.2007)	0.106 (0.1687)	0.098 (0.1411)	0.079 (0.1627)	0.076 (0.1442)	0.078 (0.1562)
Median	0.09	0.12	0.10	0.06	0.05	0.05	0.05
Min, max	-0.41, 0.70	-0.30, 0.78	-0.13, 0.87	-0.16, 0.37	-0.27, 0.90	-0.18, 0.57	-0.27, 0.90

Only subjects with non-missing data at both Baseline and the relevant post-Baseline visit are included in the change from Baseline summary statistics.

Bayesian Analysis on ADCOMS at 12 Months is presented below.

Table CE7: Bayesian analysis of ADCOMS at 12 months – FAS

		Change from Baseline		Posterior Quantities			
Treatment Group	Total N	Mean	SD	Pr (Max)	Pr (ED_{90})	Pr Superiority	Pr (CSD)
ADCOMS – Overall							
Placebo control	238	0.113	0.012	-	-	-	-
2.5 mg/kg biweekly	52	0.134	0.024	0.009	0.009	0.216	0.028
5 mg/kg monthly	48	0.119	0.021	0.022	0.031	0.416	0.070
5 mg/kg biweekly	89	0.116	0.016	0.010	0.010	0.446	0.053
10 mg/kg monthly	246	0.084	0.011	0.318	0.386	0.961	0.479
10 mg/kg biweekly	152	0.077	0.014	0.642	0.563	0.976	0.638

ADCOMS = Alzheimer's Disease Composite Score, CSD = clinically significant difference, ED_{90} = dose regimen with at least 90% of the d_{max} treatment effect, Max = maximum, Pr = probability.

Conventional Analysis on ADCOMS at 12 Months is presented below, in the full population, by ApoE4 status and by clinical status.

Table CE8: Summary of MMRM Analyses of Change from Baseline in ADCOMS at 12 Months – FAS

	Individual Treatment Groups Analysis						Combined Analysis	
		BAN2401						BAN2401
Parameter Visit Statistic	Placebo (N=238)	2.5 mg/kg Biweekly (N=52)	5 mg/kg Monthly (N=48)	5 mg/kg Biweekly (N=89)	10 mg/kg Monthly (N=246)	10 mg/kg Biweekly (N=152)	Placebo (N=238)	Combined 10 mg/kg Monthly and Biweekly (N=398)
ADCOMS – Overall								
Week 53 (Month 12)								
n	187	38	42	67	165	93	187	258
LS mean	0.131	0.158	0.149	0.139	0.102	0.085	0.128	0.093
SE	0.013	0.027	0.027	0.021	0.014	0.017	0.013	0.012
LS mean difference: active dose – placebo	-	0.028	0.019	0.008	-0.029	-0.046	-	-0.035
90% CI for differences	-	-0.020, 0.076	-0.029, 0.066	-0.030, 0.046	-0.057, 0.000	-0.079, -0.012	-	-0.060, -0.010
P-value	-	0.336	0.514	0.731	0.101	0.027	-	0.019

The change from Baseline for each parameter in overall population was analyzed using the MMRM with treatment group/combined treatment group, visit, disease stage (MCI due to AD, mild AD dementia), ApoE4 status (carrier, non-carrier), presence or absence of concomitant AD treatment (AChEIs and/or memantine) at Baseline, region, treatment group-by-visit interaction as factors, and Baseline value as covariate. The mixed-effects model within each randomization stratum (subgroup) was similar and was reduced by removing corresponding stratification factor from the model in overall population. Subjects were censored at the time of initiation or change of AChEIs or memantine treatment regimens.
AChEIs = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADCOMS = Alzheimer's Disease Composite Score, ApoE4 = apolipoprotein ϵ4 variant, LS = least square, MCI = mild cognitive impairment, MMRM = mixed-effects model with repeated measures.

The row labelled 'n' reflects the number of subjects who had an ADCOMS assessment at Week 53 (Month 12).

Table CE9: Summary of MMRM Analyses of Change from Baseline in ADCOMS at 12 Months by ApoE4 status – FAS

		BAN2401				
Visit Strata Level Statistic	Placebo (N = 238)	2.5 mg/kg bi-Weekly (N = 52)	5 mg/kg Monthly (N = 48)	5 mg/kg bi-Weekly (N = 89)	10 mg/kg Monthly (N = 246)	10 mg/kg bi-Weekly (N = 152)
Week 53						
ApoE4 Positive						
n	134	26	32	61	145	11
Least Square Mean	0.136	0.155	0.134	0.131	0.097	0.044
SE	0.016	0.039	0.031	0.022	0.015	0.041
LS Mean Difference: Active Dose - Placebo		0.019	-0.002	-0.004	-0.039	-0.091
90% Confidence Interval for Differences		-0.038, 0.077	-0.057, 0.053	-0.046, 0.037	-0.071, -0.007	-0.161, -0.022
p-value		0.578	0.952	0.862	0.048	0.031
ApoE4 Negative						
n	53	12	10	6	20	82
Least Square Mean	0.120	0.165	0.195	0.195	0.124	0.107
SE	0.024	0.049	0.055	0.067	0.038	0.021
LS Mean Difference: Active Dose - Placebo		0.045	0.075	0.075	0.003	-0.014
90% Confidence Interval for Differences		-0.048, 0.132	-0.022, 0.171	-0.040, 0.190	-0.068, 0.074	-0.061, 0.034
p-value		0.398	0.202	0.284	0.938	0.639

Table CE10: Summary of MMRM Analyses of Change from Baseline in ADCOMS at 12 Months by Clinical status - FAS

Visit Strata Level Statistic	Placebo (N = 238)	BAN2401 2.5 mg/kg bi-Weekly (N = 52)	BAN2401 5 mg/kg Monthly (N = 48)	BAN2401 5 mg/kg bi-Weekly (N = 89)	BAN2401 10 mg/kg Monthly (N = 246)	BAN2401 10 mg/kg bi-Weekly (N = 152)
Week 53						
MCI due to AD						
n	128	25	31	41	113	50
Least Square Mean	0.109	0.124	0.113	0.119	0.084	0.078
SE	0.014	0.028	0.026	0.022	0.015	0.019
LS Mean Difference: Active Dose - Placebo		0.015	0.005	0.010	-0.024	-0.031
90% Confidence Interval for Differences		-0.033, 0.063	-0.040, 0.050	-0.029, 0.050	-0.052, 0.004	-0.066, 0.005
p-value		0.604	0.866	0.664	0.159	0.161
Mild AD						
n	59	13	11	26	52	43
Least Square Mean	0.163	0.210	0.235	0.159	0.119	0.077
SE	0.029	0.059	0.067	0.043	0.032	0.034
LS Mean Difference: Active Dose - Placebo		0.047	0.072	-0.004	-0.044	-0.086
90% Confidence Interval for Differences		-0.059, 0.154	-0.045, 0.190	-0.085, 0.078	-0.110, 0.023	-0.157, -0.015
p-value		0.464	0.311	0.938	0.278	0.046

The primary endpoint was not met: The primary Bayesian analysis of ADCOMS at week 53 indicated that the 10mg/kg biweekly dose had a 64% probability of being superior to placebo by a clinically significant difference of 25%, which did not meet the prespecified criterion for success of 80%.

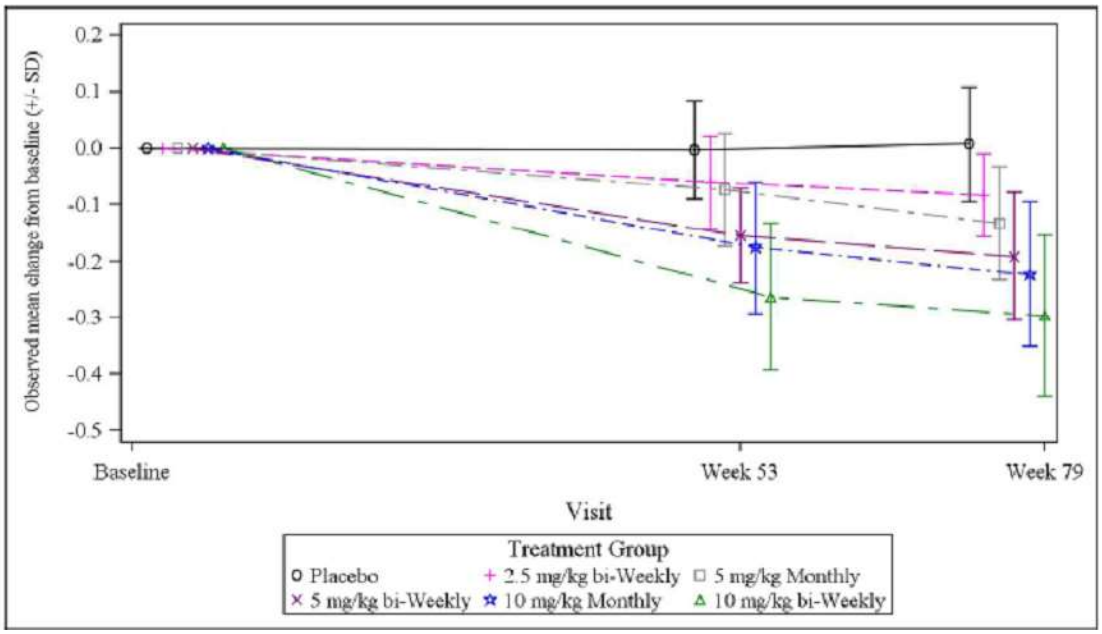
Subgroup analysis by ApoE4 status reveals a larger effect size in ApoE4 carriers compared with non-carriers, despite similar amyloid reductions observed in both carriers and non-carriers. The opposite was seen in study 301 with a larger effect seen in non-carriers, as discussed further below.

Subgroup analysis by clinical status showed a larger effect size in subjects with mild AD compared with those with MCI due to AD.

Key Secondary endpoints

- Change from Baseline at 18 months in brain amyloid pathophysiology as measured by amyloid PET.

Figure CE1: Observed Mean (SD) Change from Baseline in Brain Amyloid Levels as Measured by Amyloid PET SUVr Normalized to Whole Cerebellum Mask by Visit - Overall - PD Analysis Set 2



In the voluntary PET sub study, 315 subjects had sufficient amyloid PET data to derive at least 1 amyloid PET parameter (PD analysis set 2); 99 in the placebo group and 216 in the lecanemab groups. A significant dose and time dependant reduction of brain amyloid plaque was seen with lecanemab treatment, with the greatest reduction in the 10 mg/kg biweekly group. In comparison a slight increase was seen in the placebo group. Significant amyloid plaque reduction was seen across patient demographic and disease characteristics.

- Change from Baseline in ADCOMS at 18 months.

Conventional analysis in ADCOMS at 18 months is presented below.

Table CE11: Summary of MMRM analyses of change from baseline in ADCOMS at 18 months – FAS

	Individual Treatment Groups Analysis						Combined BAN2401 10 mg/kg Treatment Groups Analysis	
		BAN2401						BAN2401
Parameter Visit Statistic	Placebo (N=238)	2.5 mg/kg Biweekly (N=52)	5 mg/kg Monthly (N=48)	5 mg/kg Biweekly (N=89)	10 mg/kg Monthly (N=246)	10 mg/kg Biweekly (N=152)	Placebo (N=238)	Combined 10 mg/kg Monthly and Biweekly (N=398)
ADCOMS – Overall								
Week 79 (Month 18)								
n	160	33	35	61	146	79	160	225
LS mean	0.193	0.173	0.192	0.199	0.166	0.136	0.190	0.152
SE	0.017	0.035	0.035	0.026	0.018	0.022	0.017	0.014
LS mean difference: active dose – placebo	-	-0.020	-0.001	0.006	-0.028	-0.057	-	-0.039
90% CI for differences	-	-0.083, 0.042	-0.064, 0.061	-0.044, 0.055	-0.065, 0.010	-0.102, -0.013	-	-0.071, -0.006
P-value	-	0.592	0.971	0.855	0.228	0.034	-	0.053

Change from Baseline for each parameter in overall population was analyzed using MMRM with treatment group/combined treatment group, visit, disease stage (MCI due to AD, mild AD dementia), ApoE4 status (carrier, non-carrier), presence or absence of concomitant AD treatment (AChEIs and/or memantine) at Baseline, region, treatment group-by-visit interaction as factors, and Baseline value as covariate. The mixed-effects model within each randomization stratum (subgroup) was similar and was reduced by removing corresponding stratification factor from the model in overall population. Subjects were censored at the time of initiation or change of AChEIs or memantine treatment regimens.

The greatest treatment effect was seen in the 10 mg/kg biweekly group with a LS mean difference from placebo of -0.057 representing 30% less decline than in the placebo group. Whilst no effect was seen in the 5 mg/kg monthly or biweekly groups, unexpectedly, a similar treatment effect was seen in the 2.5 mg/kg biweekly group as the 10 mg/kg monthly group, albeit lower than the effect seen in the 10 mg/kg biweekly group.

The 10 mg/kg biweekly dose had a 76% probability of being superior to placebo by a clinically significant difference of 25%, which did not meet the prespecified criterion for success of 80%.

- Change from Baseline in CDR-SB at 18 months.

Conventional analysis in CDR-SB is presented below.

Table CE12: Summary of MMRM analyses of change from baseline in CDR-SB at 18 months – FAS

Parameter Visit Statistic	Individual Treatment Groups Analysis						Combined BAN2401 10 mg/kg Treatment Groups Analysis	
		BAN2401						BAN2401
	Placebo (N=238)	2.5 mg/kg Biweekly (N=52)	5 mg/kg Monthly (N=48)	5 mg/kg Biweekly (N=89)	10 mg/kg Monthly (N=246)	10 mg/kg Biweekly (N=152)	Placebo (N=238)	Combined 10 mg/kg Monthly and Biweekly (N=398)
CDR-SB – Overall								
Week 79 (Month 18)								
n	161	34	36	67	149	84	161	233
LS mean	1.499	1.227	1.713	1.463	1.248	1.102	1.473	1.171
SE	0.16	0.338	0.334	0.250	0.169	0.213	0.158	0.136
LS mean difference: active dose – placebo	-	-0.271	0.214	-0.036	-0.250	-0.396	-	-0.302
90% CI for differences	-	-0.875, 0.332	-0.384, 0.812	-0.510, 0.439	-0.613, 0.112	-0.821, 0.028	-	-0.620, 0.017
P-value	-	0.459	0.555	0.901	0.255	0.125	-	0.119

The greatest treatment effect was seen in the 10 mg/kg biweekly group with a LS mean difference from placebo of -0.396 representing 26% less decline than in the placebo group. A similar trend to ADCOMS was seen in terms of the results in the 2.5 mg/kg biweekly and 10mg/kg monthly group.

- Change from Baseline in ADAS–Cog14 at 18 months.

Conventional analysis in ADAS-Cog14 is presented below.

Table CE13: Summary of MMRM analyses of change from baseline in ADAS-Cog14 at 18 months – FAS

Parameter Visit Statistic	Individual Treatment Groups Analysis						Combined BAN2401 10 mg/kg Treatment Groups Analysis	
		BAN2401						BAN2401
	Placebo (N=238)	2.5 mg/kg Biweekly (N=52)	5 mg/kg Monthly (N=48)	5 mg/kg Biweekly (N=89)	10 mg/kg Monthly (N=246)	10 mg/kg Biweekly (N=152)	Placebo (N=238)	Combined 10 mg/kg Monthly and Biweekly (N=398)
ADAS–Cog14 – Overall								
Week 79 (Month 18)								
n	158	33	34	61	146	79	158	225
LS mean	4.902	5.574	5.746	4.506	4.624	2.588	4.799	3.735
SE	0.617	1.275	1.279	0.959	0.652	0.811	0.633	0.549
LS mean difference: active dose – placebo	-	0.672	0.844	-0.395	-0.278	-2.313	-	-1.064
90% CI for differences	-	-1.586, 2.930	-1.422, 3.111	-2.192, 1.401	-1.635, 1.079	-3.910, -0.717	-	-2.290, 0.163
P-value	-	0.624	0.539	0.717	0.736	0.017	-	0.154

The greatest treatment effect was seen in the 10 mg/kg biweekly group with a LS mean difference from placebo of -2.313 representing 47% less decline than in the placebo group.

The difference in effect in the 10 mg/kg biweekly group compared with any of the other lecanemab treatment groups was more pronounced with the ADAS-Cog14 than for ADCOMS or CDR-SB and no effect was seen in the 2.5 mg/kg biweekly group

- Change from Baseline in CSF biomarkers (including Aβ[1-42], t-tau, and p-tau) at 18 months.

In the voluntary CSF substudy, CSF Aβ(1-42) was measured to evaluate whether target engagement of lecanemab lead to an expected increase in total CSF Aβ monomer levels. P-tau and t-tau were measured to explore the effects of lecanemab on downstream tau pathology.

Ninety-two subjects had sufficient CSF data to derive at least 1 CSF parameter (PD analysis set 3); 24 in the placebo group and 68 in the lecanemab groups. Due to attrition rates in this substudy that already had a low number of participants, in the 10 mg/kg biweekly group data was only available in 9 subjects at 12 months and 8 subjects at 18 months.

Observed mean change from baseline in CSF Aβ[1-42], total-tau, and phospho-tau are presented below.

Figure CE2: Observed Mean Change From Baseline in CSF Aβ(1-42) pg/mL by Visit for Individual Treatment Groups (Placebo and BAN2401) - PD Analysis Set 3

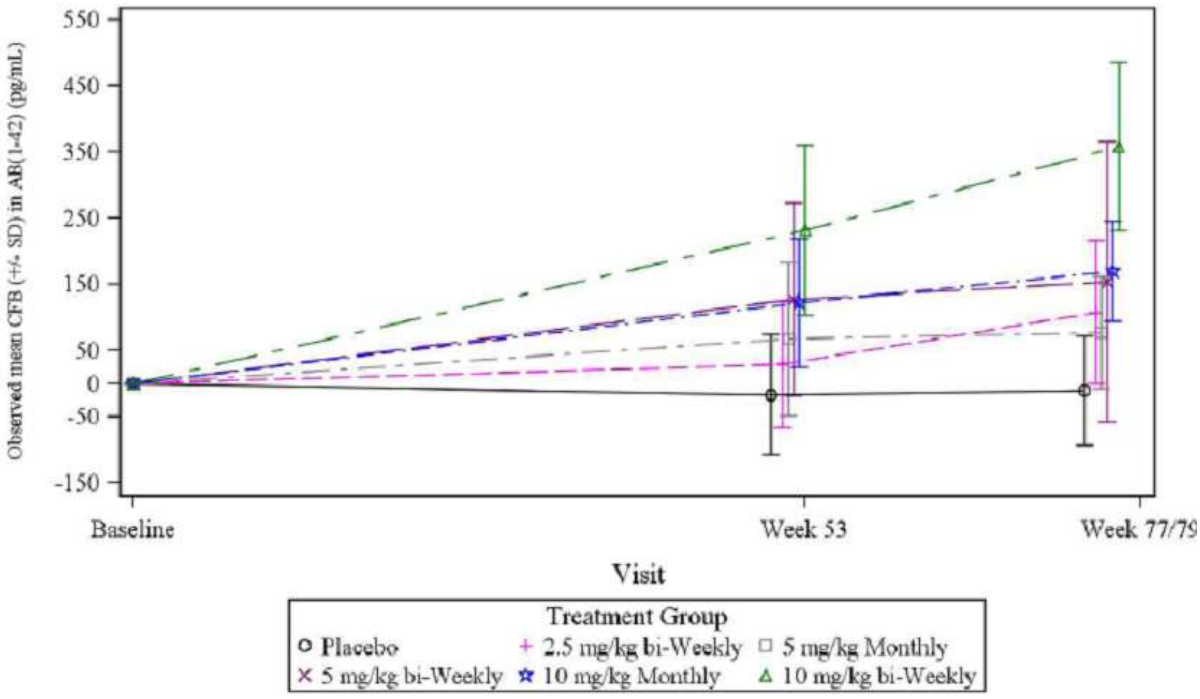


Figure CE3: Observed Mean Change from Baseline in CSF t-tau pg/mL by Visit for Individual Treatment Groups (Placebo and BAN2401) - PD Analysis Set 3

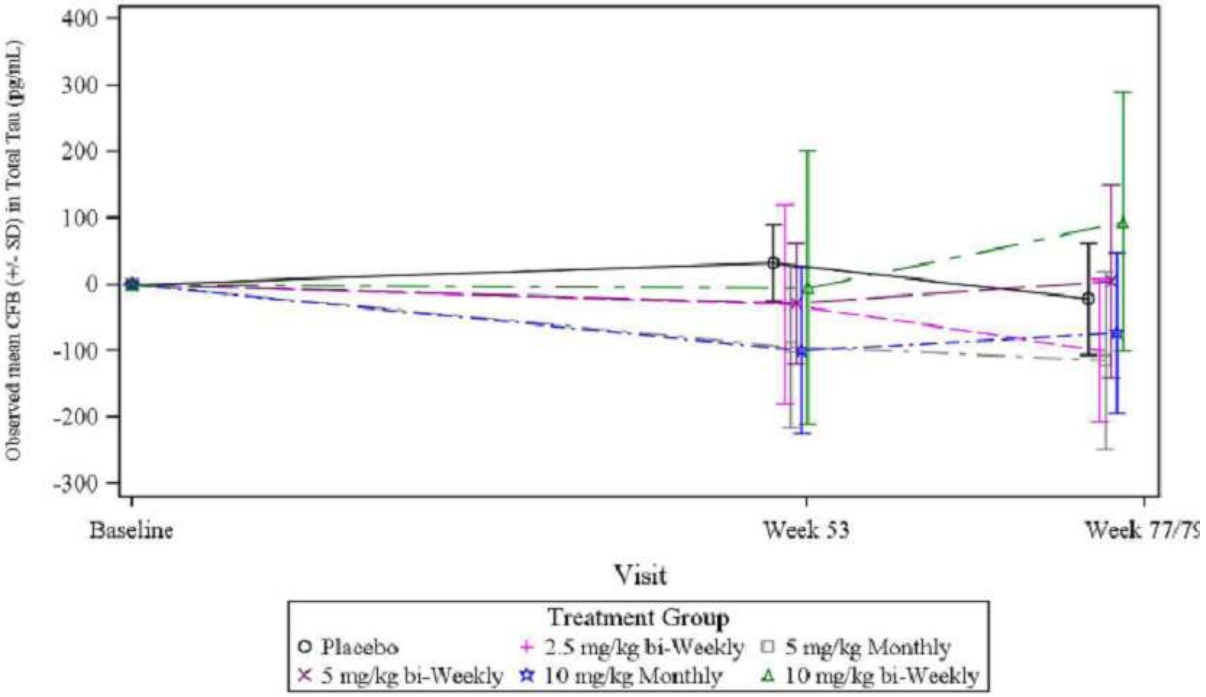
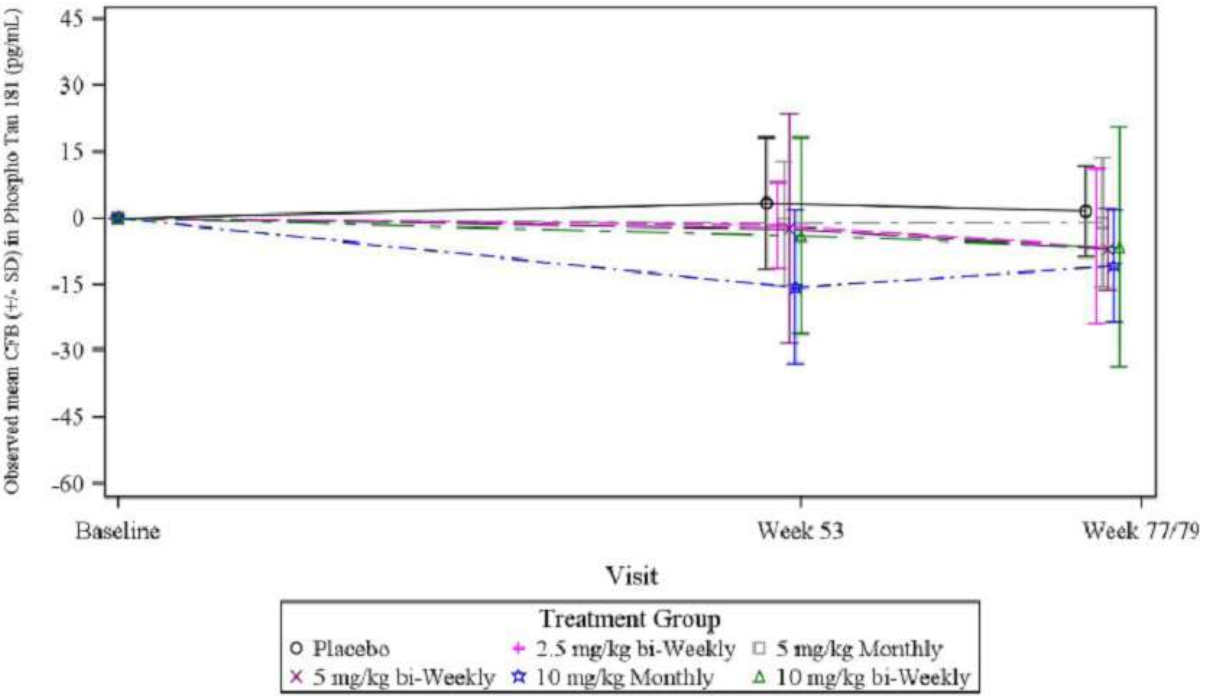


Figure CE4: Observed Mean Change from Baseline in CSF p-tau pg/mL by Visit for Individual Treatment Groups (Placebo and BAN2401) – PD Analysis Set 3



- Change from Baseline in total hippocampal volume at 18 months using vMRI.

Table CE14: Summary of MMRM Analyses of Change from Baseline in Total Hippocampal Volume at 18 Months - PD Analysis Set 1

Parameter Visit Statistic	Individual Treatment Groups Analysis						Combined BAN2401 10 mg/kg Treatment Groups Analysis	
		BAN2401						BAN2401
	Placebo (N=209)	2.5 mg/kg Biweekly (N=41)	5 mg/kg Monthly (N=46)	5 mg/kg Biweekly (N=73)	10 mg/kg Monthly (N=188)	10 mg/kg Biweekly (N=99)	Placebo (N=209)	Combined 10 mg/kg Monthly and Biweekly (N=287)
Total Hippocampus Volume – Overall								
Week 79 (Month 18)								
n	162	34	39	55	144	72	162	216
LS mean	-257.297	-305.254	-304.600	-297.469	-264.868	-276.740	-255.321	-266.644
SE	10.394	20.161	19.053	15.955	11.448	14.681	11.046	10.321
LS mean difference: active dose – placebo	-	-47.958	-47.304	-40.173	-7.572	-19.443	-	-11.324
90% CI for differences	-	-82.366, -13.549	-79.974, -14.634	-68.411, -11.934	-28.421, 13.278	-46.770, 7.883	-	-30.434, 7.787
P-value[a]	-	0.022	0.017	0.019	0.550	0.242	-	0.330
Dunnett *P*-value[b]	-	0.328	0.269	0.296	1.000	0.993	-	0.909

There was no difference in observed mean vMRI total hippocampal volume change from baseline at 18 months with either lecanemab 10 mg/kg monthly or biweekly compared to placebo. However, greater reductions in whole brain volume and greater increases in ventricular volume were seen in all subjects on lecanemab at 18 months compared with placebo (exploratory endpoints). Whilst no clear dose response was seen, the greatest reduction was seen in the 10 mg/kg biweekly dose group. This phenomenon was also observed in the pivotal phase 3 study (discussed further below).

Summary of the results of study 201 core

Whilst the primary endpoint was not met, the largest size effect in change from baseline compared with placebo was seen in the 10mg/kg biweekly group. For all 3 secondary efficacy endpoints, the greatest treatment effect was seen in the lecanemab 10mg/kg biweekly group. Conversely to the results in the pivotal study 301, subgroup analysis by ApoE4 status revealed a larger effect size in ApoE4 carriers compared with non-carriers

A significant dose and time dependant reduction of brain amyloid plaque was seen with lecanemab treatment, with the greatest reduction in the 10mg/kg biweekly group. Whereas a slight increase was seen in the placebo group.

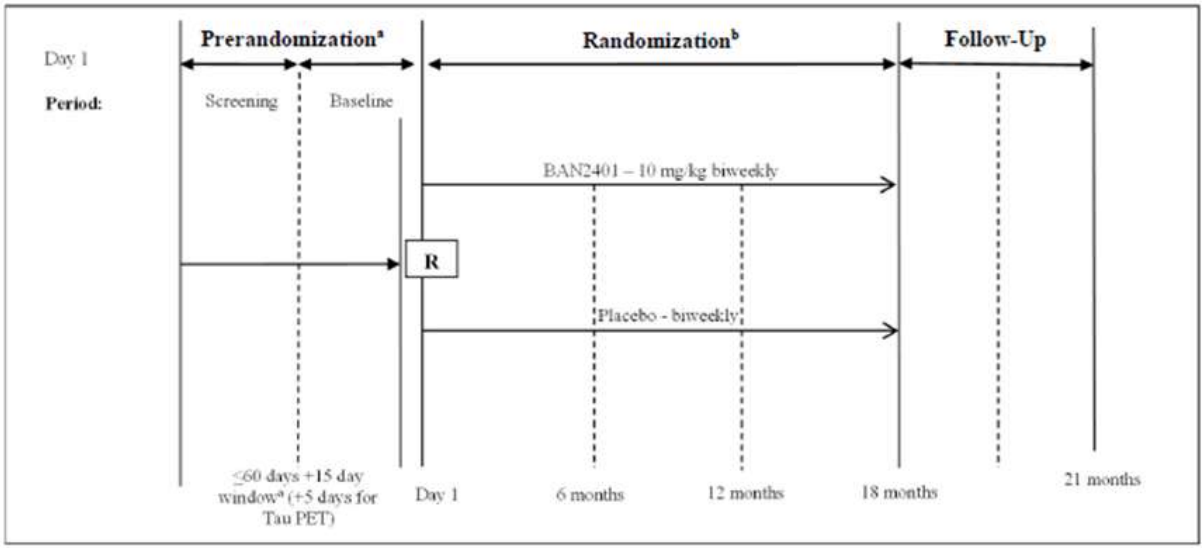
Overall, the results of this dose-finding study support the decision to take forward the 10 mg/kg biweekly dose into the pivotal phase 3 study.

Main study
BAN2401-G000-301 (301) -pivotal Phase III study

This was a placebo-controlled, double-blind, parallel-group, 18-month study with an open-label extension phase to confirm safety and efficacy of BAN2401 in subjects with early Alzheimer's disease.

Methods

Figure CE5: Design of Study 301 - Core



There were 3 longitudinal substudies during the Core Study: amyloid PET, CSF biomarker assessments, and tau PET. Participation in these substudies was optional.

At the end of the Core Study, subjects who completed 18 months of study drug treatment had the option of enrolling into the open-label extension (OLE) Phase, provided they met the inclusion/exclusion criteria.

Note: Data from the Core Study, excluding data from the subjects randomised in China, was locked, unblinded, and analysed after all subjects (except the subjects randomised in China) completed their final Core Study treatment visit. No data from subjects randomised in China are included in the current version of the clinical study report, as the database is still blinded for these subjects.

Study participants
Inclusion criteria
Diagnosis
MCI due to AD-intermediate likelihood:
1. Met the NIA-AA core clinical criteria for MCI due to AD-intermediate likelihood.
2. Had a global CDR score of 0.5 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline.
3. Reported a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; must have to be corroborated by an informant.

Mild AD dementia:
4. Met the NIA-AA core clinical criteria for probable AD dementia.

5. Had a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline.

Key inclusion criteria

- 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 (subscale) II (WMS-IV LMII).
- Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
  a. PET assessment of imaging agent uptake into brain. Note: amyloid PET screens were to be performed according to local regulatory guidelines and thus, in some regions, were restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
  b. CSF assessment of t-tau/Aβ[1-42].
- Male or female subjects ≥50 and ≤90 years, at the time of informed consent.
- MMSE score greater than or equal to 22 at Screening and Baseline and less than or equal to 30 at Screening and Baseline.
- Body mass index greater than 17 and less than 35 at Screening.
- If subjects were receiving an approved AD treatment, such as AChEIs, or memantine, or both for AD, they had to have been on a stable dose for at least 12 weeks prior to Baseline. Treatment-naïve subjects for AD medications could be enrolled into the study.
- Have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject).

Main exclusion criteria

- Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD.
- History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening.
- Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the subject.
- GDS score greater than or equal to 8 at Screening.
- Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD.
- Other significant pathological findings on brain MRI at Screening including but not limited to: more than 4 microhaemorrhages; a single macrohaemorrhage greater than 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic oedema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumours.
- Hypersensitivity to BAN2401 or any of the excipients, or to any monoclonal antibody treatment.
- Subjects with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5 for subjects who are not on anticoagulant treatment, e.g., warfarin). Subjects who were on anticoagulant therapy had to have their anticoagulant status optimised and be on a stable dose for 4 weeks before Screening.
- Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or ECG at Screening or Baseline which in the opinion of the

investigator require further investigation or treatment or which may interfere with study procedures or safety.

ApoE4 non-carriers and ApoE4 carriers were allowed to enter in the study, ApoE4 status being a major genetic determinant of Alzheimer's disease.

Subjects receiving an approved symptomatic treatment for AD at baseline could be enrolled if they had been on a stable dose for at least 12 weeks prior to baseline. This is acceptable in the context of a study for a disease modifying treatment and ongoing treatment with concurrent mediations for AD was a stratification factor.

The SmPC reflects the key inclusion/exclusion criteria in study 301 and the criteria for demonstrating the presence of Aβ brain pathology.

Treatments

Active

Lecanemab was administered at a dose of 10 mg/kg. Subjects received biweekly infusions (i.e. every two weeks). Lecanemab was administered in normal saline as approximately 60-minute intravenous infusions. The dose was selected based on the results of the 201 study.

Placebo

Matching placebo was 0.9% sodium chloride, to be sourced by each site and used in accordance with the administration instructions provided.

Objectives and endpoints

Primary Objective

- To evaluate the efficacy of lecanemab 10 mg/kg bi-weekly (LEC10-BW) in subjects with early Alzheimer's disease (EAD) by determining the superiority of LEC10-BW compared with placebo on the change from baseline in the CDR-SB at 18 months of treatment.

Primary Endpoint

- Change from baseline in CDR-SB at 18 months.

Key Secondary Endpoints

- Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels.
- Change from baseline in ADAS-Cog14 at 18 months.
- Change from baseline in ADCOMS at 18 months.
- Change from baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 18 months.

Biomarker endpoints

Key biomarker and PD endpoints included:

- Correlation between clinical changes and changes in amyloid PET SUVR composite for brain amyloid levels
- Change from baseline in tau PET.
- Change from baseline in blood and CSF biomarkers (Aβ[1-42], Aβ[1-40], plasma Aβ42/40 ratio, neurogranin [CSF only], NfL, t-tau, and p-tau [including but not limited to p-tau181]) at 12 and 18 months.

- Change from baseline in brain volumes as measured by volumetric magnetic resonance imaging (vMRI).

Exploratory endpoints
Exploratory endpoints included:

- Change from baseline in European Quality of Life-5 Dimensions 5-Level version (EQ-5D-5L), Quality of Life in Alzheimer's Disease (QOL-AD), and Zarit Burden Interview (ZBI) at 18 months
- Time to worsening of global Clinical Dementia Rating (CDR) score by 18 months

ADCS MCI-ADL
The ADCS MCI-ADL is a questionnaire for informants that consists of 17 instrumental items (such as shopping, preparing meals, and using household appliances) and 1 basic item (getting dressed) intended to reflect activities of daily living. The total score can range between 0 and 53, with lower values indicating greater impairment.

Sample size
The sample size for this study was estimated based on comparison of LEC10-BW and placebo with respect to the primary efficacy endpoint, the change from baseline in CDR-SB at 18 months. Based on data from Study 201, the estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo was 2.031 and the estimated treatment difference was 0.373 in all subjects. Therefore, assuming an estimated 20% dropout rate at 18 months in this study, a total sample size of 1566 subjects (including 783 subjects in placebo and 783 subjects in LEC10-BW) had 90% power to detect the treatment difference between placebo and LEC10-BW in all subjects using a 2-sample t test at a significance level of 2-sided alpha=0.05.

Approximately 200 subjects missed 3 or more consecutive doses due to the COVID-19 pandemic. In agreement with the FDA in December 2020, approximately 200 additional subjects were randomised to retain 90% power which resulted in a total sample size of approximately 1766 randomised subjects. To ensure consistency of the study population with prior data used in the specified power calculations, approximately 70% of the total number of subjects randomised were ApoE4 carriers.

No interim analysis was planned or conducted for this study.

Randomisation
Subjects were assigned to treatments, (allocated 1:1; placebo: lecanemab), based on a computer-generated randomisation scheme that was reviewed and approved by an independent statistician.

Subjects were stratified by clinical subgroup (MCI or mild AD dementia), ApoE4 status (carrier or non-carrier), ongoing treatment with AD medications (yes or no) and geographic region (North America, Europe, or Asia Pacific).

Randomisation was performed centrally by an interactive voice and web response system. Randomisation was managed to ensure that approximately 70% of the total number of subjects randomised would be ApoE4 carriers. Additionally, no less than 50% of subjects were to be in the MCI due to AD clinical subgroup.

Blinding (masking)

During the Randomisation Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff were blinded to the treatment codes. Randomisation data was kept strictly confidential, filed securely by an appropriate group with the sponsor or contract research organization (CRO) and accessible only to authorized persons (e.g., Eisai Global Safety) until the time of unblinding.

In the event that emergency conditions required knowledge of the study drug given, the blind could be broken via the code breaker facility. The investigator was instructed to consult with the sponsor about the medical necessity before breaking the blind, if possible. An independent, blinded medical monitoring team, firewalled from the clinical study team to prevent bias, reviewed amyloid-related imaging abnormalities (ARIA), infusion-related reactions and hypersensitivity reactions. Investigators responsible for the medical management of participants were independent from those involved in rating clinical assessments.

Statistical methods

Definitions of analysis populations

Table CE15: Analysis populations in study 301 CORE

Population	Description
Randomised set	All randomised subjects.
Safety analysis set (SAS)	Randomised subjects who received at least 1 dose of the study drug. At least 1 post-dose laboratory, vital sign or ECG measurement is required for inclusion in analysis of these specific parameters. Subjects were required to have baseline measurements to be included in any analyses examining changes from baseline. This population is used for all safety analyses which will be based on the as-treated principle.
Full analysis set (FAS+)	Randomised subjects who received at least 1 dose of the study drug and had a baseline assessment as well as at least 1 post-dose primary efficacy measurement.
FDA Full analysis set (FDA FAS)	Randomised subjects who received at least 1 dose of the study drug, had a baseline assessment as well as at least 1 post-dose primary efficacy measurement, and were not randomised on or before the dosing hold end date at sites with a dosing hold ≥42 days (equivalent to 3 consecutive doses) during the covid period of 01.03.2020-31.07.2020.
Per protocol analysis set (PP)	Subjects in FDA FAS who did not miss 3 or more consecutive doses during the first 6 months in the study.
PK analysis set	Subjects with at least one quantifiable BAN2401 serum concentration or CSF concentration with a documented dosing history.
PD analysis set	Subjects who received at least 1 dose of study drug and have sufficient PD data to derive at least one PD parameter (baseline and at least 1 post-dose assessment).

Primary efficacy analysis

The primary analysis population for EU/GB was the FAS+ set.

The null hypothesis for this analysis was that there was no difference in the mean change from baseline CDR-SB at 18 months between LEC10-BW and placebo at a significance level of two-sided α=0.05.

A mixed-effects model with repeated measures (MMRM) was used to estimate the mean difference of the change from baseline in CDR-SB between subjects treated with LEC10-BW and subjects treated with placebo. All observed data were included in the analysis, including any data collected after intercurrent events such as the initiation of new concomitant treatments for AD, change of concomitant treatments for AD, or treatment discontinuation. No imputation of missing values was carried out; the MMRM automatically handles missing data under a missing at random assumption. The MMRM included baseline CDR-SB as a covariate, with treatment group, visit, clinical subgroup, use of AD symptomatic medication at baseline, ApoE4 carrier status, geographical region, baseline CDR-SB-by-visit, and treatment group-by-visit interaction as fixed effects. Adjusted means and adjusted mean difference between LEC10-BW and placebo were presented alongside the corresponding 95% CIs.

Sensitivity and supplementary analyses of the primary endpoint were conducted.

Key secondary analyses
If the primary endpoint was found to be statistically significant, the key secondary endpoints were tested in a pre-specified hierarchy as shown below. Each test was two-sided, with α=0.05, and was only performed if the preceding test was statistically significant.

Table CE16: Analyses of key secondary endpoints

Key secondary analysis endpoints	Hierarchy
Change from baseline in amyloid PET using centiloids at 18 months for brain amyloid levels	1 (tested first)
Change from baseline in ADAS-Cog14 at 18 months	2
Change from baseline in ADCOMS at 18 months	3
Change from baseline in ADCS MCI-ADL at 18 months	4 (tested last)

For all key secondary analyses, the MMRM model was used as in the primary analysis. The only difference was that instead of including baseline CDR-SB and baseline CDR-SB-by-visit interaction in the model, the model included the baseline of the relevant response variable (i.e. baseline amyloid PET using Centiloids, baseline ADAS-Cog14, baseline ADCOMS, or baseline ADCS MCI-ADL) and the baseline of the response variable -by-visit interaction (baseline amyloid PET using Centiloids-by-visit-interaction, baseline ADAS-Cog14-by-visit-interaction, baseline ADCOMS-by-visit-interaction, or baseline ADCS MCI-ADL-by-visit-interaction).

Exploratory efficacy analysis

Table CE17: Analyses of exploratory endpoints

Exploratory analysis endpoints	Methods
Change from baseline in modified iADRS at 18 months	Analysed using the same MMRM as in the primary analysis. Baseline modified iADRS and baseline modified iADRS-by-visit were used in the model instead of baseline CDR-SB and baseline CDR-SB-by-visit. Subgroup analyses, including an analysis in ApoE4 carriers, were also carried out.
Rate of change over time (mean slope) based on change from baseline in the CDR-SB	Rate of change over time (mean slope) based on change from baseline in CDR-SB was analysed using a linear mixed effects (LME) model for multivariate normal data derived from a random coefficient model (slope analysis) where the mean slope depends on continuous assessment time. The LME model included assessment time, and treatment group-by-assessment time as covariates with random intercept and slope.
Time to worsening of global CDR scores by 18 months	Time to worsening of global CDR scores by 18 months was analysed using Cox regression adjusted for stratification variables. Time to worsening of a global CDR score is defined as time from randomization to first worsening of the global CDR score. For subjects whose global CDR scores were not worse by the end of study, the time to worsening was censored at the date of the last CDR assessment. Median, 1st quartile, 3rd quartile of time to worsening of global CDR scores and proportion of subjects with worsening of global CDR scores at 3, 6, 9, 12, 15, and 18 months were estimated using Kaplan-Meier.
Change from baseline in EQ-5D-5L, QOL-AD, and Zarit Burden Interview at 18 months	Change from baseline in EQ-5D-5L, QOL-AD, and Zarit Burden Interview was analysed using MMRM as in the primary analysis, using the baseline of the response variable and the baseline of the response variable -by-visit interaction instead of baseline CDR-SB and baseline CDR-SB-by-visit interaction.
Relationship of PK exposure with blood and CSF biomarkers, safety parameters, and efficacy	Relationship of PK exposure with blood and CSF biomarkers, safety parameters, and efficacy (mainly CDR-SB) was evaluated.

Biomarker analyses

Biomarker endpoints were analysed using the PD Analysis Set. Tests were two-sided with an α=0.05. Analysis by subgroups of interest were also performed.

1. For the following endpoints, analyses were carried out using the MMRM as specified for the primary analysis except that the model included the baseline value corresponding to the response variable and the baseline value for the response variable-by-visit interaction instead of baseline CDR-SB and baseline CDRSB-by-visit interaction:
    a. Change from baseline in amyloid PET SUVR composite at 3, 6, 12, and 18 and amyloid PET using Centiloids at 3, 6, and 12 months for brain amyloid levels.
    b. Change from baseline in tau PET signal as measured by tau PET SUVR in whole cortical gray matter ROI, meta-temporal ROI, frontal ROI, cingulate ROI, parietal ROI, occipital ROI, medial temporal ROI, and temporal ROI and TauIQ global tau load at 13 and 18 months.
    c. Change from baseline in blood and CSF biomarkers (including but not limited to Aβ[1-42], Aβ[1-40], Aβ42/40 ratio, neurogranin [CSF only], NFL, t-tau, and p-tau [including but not limited to p-tau181] at 12 and 18 months.
    d. Change from baseline in morphometric MRI measures (including but not limited to hippocampal volume) at 6, 12, and 18 months using vMRI.
2. For the endpoint evaluating conversion of subjects from amyloid positive to amyloid

negative (as measured by visual read, SUVR, and Centiloids) at 3, 6, 12, and 18 months, the proportion of converted subjects in each treatment arm was summarised and comparisons were carried out using the Chi-square test.

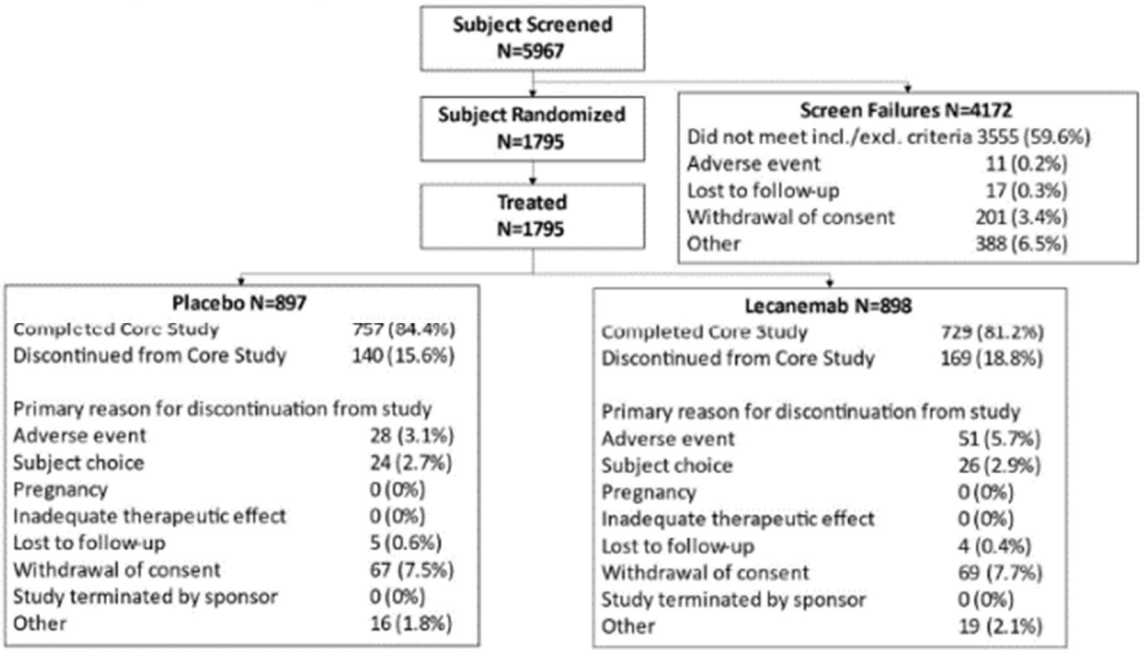
3. For endpoints evaluating the correlation between clinical changes at 18 months (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and modified iADRS) and changes in biomarkers (amyloid PET SUVR, amyloid PET using Centiloids, tau PET SUVR and TauIQ global tau load, blood and CSF biomarkers [including but not limited to Aβ[1-42], Aβ[1-40], Aβ42/40 ratio, neurogranin [CSF only], NFL, t-tau and p-tau [including but not limited to p-tau181]], and vMRI), Pearson correlations and Pearson partial correlations adjusted for baseline biomarker value and baseline clinical endpoint were carried out and p-values presented by treatment group and total. Scatter plots and regression lines were also provided. In the presence of a strong or moderate correlation, a linear model was fitted to further characterise the relationship between clinical changes and change in biomarkers. These analyses were also provided on the FAS and FAS+ analysis sets.
4. For endpoints evaluating the correlation between different biomarkers, similar analyses were conducted as in the previous point.

Summary of the design and conduct of study 301 core
Overall, the design and conduct of study 301 core is acceptable.

Results (Core)

Participant flow

Figure CE6: Disposition for study 301 – Core



There were a high proportion of screen failures (70%) at enrolment, the majority of which were due to failure to meet the inclusion/exclusion criteria with the primary reason due to patients not having early AD, based on either cognitive criteria or amyloid criteria.

A total of 1795 subjects were randomised in the study: 898 in the lecanemab group and 897 in the placebo group. All subjects received at least one dose of study drug. Of the 1795 subjects, 729 (81.2%) completed the study in the lecanemab group and 757 (84.4%) in the placebo group. The primary reason for discontinuation in the study was generally similar between the 2 groups with the exception of a slightly higher rate of discontinuations due to adverse events in the lecanemab group (5.7% vs 3.1%).

The AEs driving the observed higher discontinuation rate were infusion-related reactions and ARIA. After excluding these events, the discontinuation rate and timing in LEC10-BW were similar to placebo.

This pattern was consistent across subgroups (clinical subgroup, use of AD symptomatic medication at baseline, ApoE4 carrier status and geographical region).

Recruitment

Study 301 was conducted at 235 sites that randomised subjects in North America (112), Europe (which includes Australia, 55), Asia-Pacific (47), and China (21). No data from subjects randomised in China are included in the current version of the clinical study report, as the database is still blinded for these subjects.

Baseline data

Overall, the demographic and baseline characteristics were well balanced across the two groups.

The median age of subjects was 72 years in both groups with a range from 50 to 90 years. Twenty percent of subjects were below 65 years of age i.e., reflecting subjects with early onset of disease, 43% were ≥65 to <75 years and 37% were ≥75 years.

Just over half of subjects were female (52%). Females are more likely to have a higher tau load, particularly in early disease stages. Whilst gender was not a stratification factor, the percentage of females in both treatment groups is similar.

Most subjects were white (77%), followed by Asian (17%), with 2.6% of subjects black or African American.

In-keeping with the study design, approximately 70% (69%) of subjects were ApoE4 carriers: 53% heterozygous and 15% homozygous, with similar percentages across the 2 treatment groups. Sixty-two percent of subjects had MCI due to AD at baseline in both treatment groups (no less than 50% of subjects were to be in the MCI due to AD clinical subgroup).

Most subjects had a baseline CDR global score of 0.5 (81%) with the remainder having a score of 1 (19%). The baseline clinical endpoint scores were balanced between the 2 groups. The proportion of subjects with positive amyloid status determined by amyloid PET (lecanemab 86%; placebo 85%), and by CSF (lecanemab 29%; placebo 28%) are similar between the 2 groups. There was a slightly lower mean (SD) for global tau load, with a lower variability, for the lecanemab group (0.208 (0.1567)) compared to the placebo group (0.230 (0.2086)).

Just over half of subjects in both treatment groups were using AD symptomatic treatment at baseline. Changes in AD symptomatic treatment during the study for subjects that were on treatment at baseline were similar between the two groups. A similar percentage of subjects that were not receiving symptomatic AD treatment at baseline started treatment during the study (5% in the placebo group vs 5.5% in the lecanemab group).

The concomitant use of antithrombotic medication and type of antithrombotic medication was similar between the placebo group (33.2%) and lecanemab group (35.5%). The most commonly used antithrombotic medication was acetylsalicylic acid (25.0% vs 26.8%) followed by clopidogrel (3.2% vs 4.5%) and apixaban (3.2% vs 3.5%).

There are subpopulations of early Alzheimer’s disease that were not excluded from the study but where there are currently no data available. These include patients with Down’s syndrome and patients with atypical Alzheimer’s disease syndromes (without memory-predominant AD). This is reflected in the SmPC.

Table CE18: Demography and baseline characteristics – core study (safety analysis set)

Category	PBO (N = 897)	LEC10-BW (N = 898)	Combined Total (N = 1795)
Age (year)[a]			
n	897	898	1795
Mean (SD)	71.1 (7.79)	71.4 (7.88)	71.3 (7.83)
Min, Max	50, 90	50, 90	50, 90
Sex, n (%)			
Male	421 (46.9)	436 (48.6)	857 (47.7)
Female	476 (53.1)	462 (51.4)	938 (52.3)
Race, n (%)			
White	696 (77.6)	685 (76.3)	1381 (76.9)
Black or African American	25 (2.8)	22 (2.4)	47 (2.6)
Asian	150 (16.7)	153 (17.0)	303 (16.9)
American Indian or Alaskan Native	2 (0.2)	0	2 (0.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)	1 (0.1)
Other	12 (1.3)	21 (2.3)	33 (1.8)
Missing	12 (1.3)	16 (1.8)	28 (1.6)
APOE4 carrier status (Laboratory), n (%)			
Carriers	611 (68.1)	620 (69.0)	1231 (68.6)
Heterozygous	478 (53.3)	479 (53.3)	957 (53.3)
Homozygous	133 (14.8)	141 (15.7)	274 (15.3)
Noncarriers	286 (31.9)	278 (31.0)	564 (31.4)
Use of AD symptomatic medication at baseline (CRF), n (%)			
Yes	477 (53.2)	466 (51.9)	943 (52.5)
No	420 (46.8)	432 (48.1)	852 (47.5)
Clinical subgroup (CRF), n (%)			
MCI due to AD	555 (61.9)	552 (61.5)	1107 (61.7)
Mild AD dementia	342 (38.1)	346 (38.5)	688 (38.3)
Number of years of disease since diagnosis			
n	895	898	1793
Missing	2	0	2
Mean (SD)	1.34 (1.538)	1.43 (1.527)	1.38 (1.533)
Median	0.80	0.80	0.80
Min, Max	0, 11.2	0, 10	0, 11.2
Number of years since onset of symptoms			
n	897	897	1794
Missing	0	1	1
Mean (SD)	4.15 (2.518)	4.14 (2.354)	4.15 (2.437)
Median	3.60	3.80	3.70
Min, Max	0.5, 25.6	0.4, 21.2	0.4, 25.6
Age at onset of symptoms (Years)			
n	897	897	1794
Missing	0	1	1
Mean (SD)	67.6 (8.04)	68.0 (8.08)	67.8 (8.06)
Median	68.3	68.8	68.6
Min, Max	29.9, 86.9	38, 85.7	29.9, 86.9

Numbers analysed

Table CE19: Analysis sets (randomised set) – Core study

Analysis Set	PBO (N=897) n (%)	LEC10-BW (N=898) n (%)	Combined Total (N=1795) n (%)
Safety Analysis Set[a]	897 (100)	898 (100)	1795 (100)
Intent To Treat (Full Analysis Set+)[b]	875 (97.5)	859 (95.7)	1734 (96.6)
Intent To Treat (FDA Full Analysis Set)[c]	833 (92.9)	833 (92.8)	1666 (92.8)
Per Protocol Analysis Set[d]	799 (89.1)	730 (81.3)	1529 (85.2)
PD Analysis Set (Amyloid PET)[e]	353 (39.4)	363 (40.4)	716 (39.9)
PD Analysis Set (Tau PET)[e]	122 (13.6)	135 (15.0)	257 (14.3)
PD Analysis Set (Plasma)[e]	852 (95.0)	847 (94.3)	1699 (94.7)
PD Analysis Set (CSF)[e]	139 (15.5)	142 (15.8)	281 (15.7)
PD Analysis Set (vMRI)[e]	825 (92.0)	805 (89.6)	1630 (90.8)
PK Analysis Set (Serum)[f]	1 (0.1)	893 (99.4)	894 (49.8)
PK Analysis Set (CSF)[f]	1 (0.1)	137 (15.3)	138 (7.7)

Percentages are based on the number of randomized subjects in the relevant treatment group.
COVID-19 = coronavirus disease of 2019, CSF = cerebrospinal fluid, PET = positron emission tomography, PD = pharmacodynamic, PK = pharmacokinetic, vMRI = volumetric magnetic resonance imaging.
a: The Safety Analysis Set is the group of all allocated subjects who received at least one dose of study drug.
b: The Intent To Treat (Full Analysis Set+) is the group of randomized subjects who received at least one dose of study drug who have a baseline assessment and at least one postdose primary efficacy measurement.
c: The Intent To Treat (FDA Full Analysis Set) is the group of randomized subjects who received at least one dose of study drug, who have a baseline assessment and at least one postdose primary efficacy measurement, and who are not randomized on or before the end date of dosing hold at the sites which have dosing hold with 6 or more weeks (≥42 days, which equal to 3 consecutive doses) during COVID-19 period of 01 March to 31 July 2020.
d: The Per Protocol Analysis Set is the subset of subjects in the ITT FDA FAS who sufficiently complied with the protocol.
e: The PD Analysis Set is the group of subjects who received at least one dose of study drug, and who have sufficient PD data to derive at least one PD parameter (have baseline and at least one postdose assessment).
f: The PK Analysis Set is the group of subjects with at least one quantifiable lecanemab serum concentration (analysis set for serum) or CSF concentration (analysis set for CSF) with a documented dosing history.
Source: Table 14.1.3.1.

The percentage of subjects included in the FAS+ (primary efficacy analysis set for the EU/GB) was similar in the two treatment groups: 95.7% in the lecanemab group vs 97.5% in the placebo group.

However, fewer subjects were included in the per protocol (PP) analysis set in the lecanemab group (81.3%) compared with placebo (89.1%). In both groups the reasons for exclusion from the PP analysis set were because the 'subject is not included in the FAS', or because the 'subject missed 3 or more consecutive doses during their first 6 months in the study'.

A similar frequency of important protocol deviations was seen in the lecanemab (11.4%) and placebo (10.6%) groups. None of the important protocol deviations designated as important due to GCP violations were considered to impact the statistical analyses or interpretation and therefore did not lead to exclusion from the PP analysis set. The most common important protocol deviation was 'whole visit missing for 4 or more consecutive visits' (5.9% vs 6.7%), the majority of which were due to COVID-19.

Outcomes and estimation

Primary endpoint

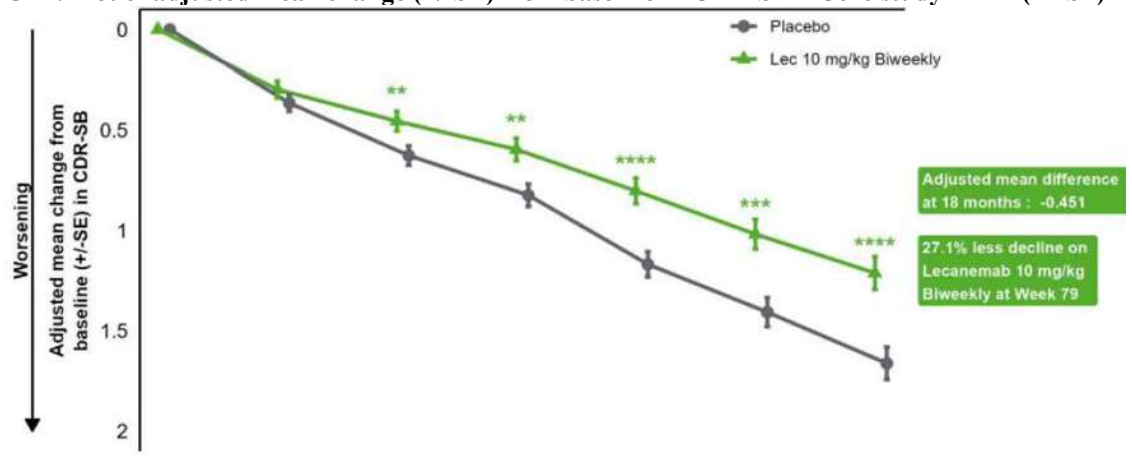
- Change from baseline in CDR-SB at 18 months

Table CE20: Change from baseline in CDR-SB score at 18 months – MMRM – Core study- intent to treat (FAS+)

Parameter Visit Statistic	PBO (N = 875)	LEC10-BW (N = 859)
CDR-SB		
Week 79		
m	875	859
n	757	714
Adjusted mean (SE)	1.663 (0.080)	1.213 (0.082)
Adjusted mean difference: Lecanemab - Placebo		-0.451
95% Confidence interval for differences		-0.669, -0.233
P-value		0.00005
% Difference vs. Placebo		-27.1%

m shows the number of subjects who are included in MMRM, n shows the number of subjects at each visit. The change from baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Missing values are not imputed and assumed to be missing at random. % difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.

Figure CE7: Plot of adjusted mean change (+/-SE) from baseline in CDR-SB – Core study – ITT (FAS+)



	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

- Sensitivity and supplemental analyses

Table CE21: Change from baseline in CDR-SB score at 18 months – MMRM - Core study (per protocol analysis set)

Parameter Visit Statistic	Placebo (N = 799)	Lecanemab 10 mg/kg Biweekly (N = 730)
CDR-SB		
Week 79		
m	799	730
n	695	614
Adjusted Mean (SE)	1.578 (0.080)	1.141 (0.084)
Adjusted Mean Difference: Lecanemab - Placebo		-0.436
95% Confidence Interval for Differences		-0.657, -0.216
P-value		0.00010
% Difference vs. Placebo		-27.7%

Table CE22: Change from baseline in CDR-SB score at 18 months – Core study – ITT – sensitivity and supplementary analyses

Type of Sensitivity or Supplementary Analysis	Adjusted Mean Change from Baseline for PBO	Adjusted Mean Change from Baseline for LEC10-BW	Adjusted Mean Difference (LEC10-BW – PBO)	95% CI for Difference	*P*-value
Rank ANCOVA with missing data imputed via multiple imputation approach Analysis set = ITT FAS+	NA	NA	-0.456*	(-0.737, -0.176)**	<0.001
Primary MMRM on all randomized subjects*** Analysis set = Randomized Set	1.659	1.225	-0.434	(-0.644, -0.224)	<0.001
Primary MMRM with randomization stratification variables based on IxRS classification Analysis set = ITT FAS+	1.669	1.217	-0.452	(-0.670, -0.234)	<0.001
Primary MMRM with log-transformed endpoint as response variable Analysis set = ITT FAS+	1.456	1.039	-0.416	NA	<0.001
Primary MMRM excluding assessments after initiation/dose adjustment of symptomatic AD drug or treatment discontinuation Analysis set = ITT FAS+	1.543	1.137	-0.406	(-0.623, -0.189)	<0.001
Primary MMRM on per-protocol participants Analysis set = per-protocol	1.578	1.141	-0.436	(-0.657, -0.216)	<0.001
Primary MMRM excluding assessments after occurrence of ARIA (ARIA-E or ARIA-H) Analysis set = ITT FAS+	1.675	1.151	-0.524	(-0.750, -0.298)	<0.001
Primary MMRM excluding assessments after occurrence of ARIA-E Analysis set = ITT FAS+	1.672	1.169	-0.503	(-0.726, -0.279)	<0.001
Primary MMRM excluding assessments after occurrence of ARIA-H Analysis set = ITT FAS+	1.661	1.162	-0.499	(-0.721, -0.277)	<0.001
Primary MMRM including APC as additional covariate Analysis set = ITT FAS+	1.633	1.150	-0.484	(-0.691, -0.276)	<0.001

The primary endpoint analysis, in the FAS+ population, demonstrated a statistically significant difference of -0.451 (95% CI: -0.669, -0.233; p=0.00005) between lecanemab and placebo in change from baseline in CDR-SB at 18 months. When considering the individual domains/items that comprise the CDR-SB, overall, a consistent effect was seen.

The FAS+ population excluded subjects who did not have at least 1 post-dose assessment and was therefore not a true ITT population. A supplementary analysis was carried out to address this which included all randomised subjects who received a dose of LEC10-BW or placebo. This supplementary analysis estimated a difference of -0.434 (95% CI: -0.644, -0.224; p<0.001) between lecanemab and placebo in change from baseline in CDR-SB at 18 months.

The results of the primary analysis are supported by results from the supplementary analysis of all randomised subjects and the results in the PP.

There was differential ascertainment of CDR-SB at week 79 for placebo and the 10 mg/kg biweekly dose. The proportion of subjects with a baseline and post-dose assessment of CDR-SB at 79 weeks, among all those treated, was 84% (757/897) in the placebo group and 79% (714/898) in the 10 mg/kg biweekly dose group.

To provide further reassurance over any potential bias resulting from missing data the primary analysis was repeated using all randomised subjects and a conservative strategy for handling of missing data (control-based multiple imputation). The results of this MMRM analysis were consistent with the main analyses, although the treatment difference was slightly smaller -0.401 (95% CI: -0.622, -0.180). Results from the equivalent analyses but with an ANCOVA were also provided and the results were reassuringly similar to the results from analyses carried out using MMRM.

Measures were in place during study 301 core to protect against functional unblinding (see methods section above) and events of ARIA and infusion-related reaction (IRR) were reported in both the lecanemab and placebo groups. However, ApoE4 homozygotes typically experience greater progression than heterozygotes or non-carriers, but this was not observed in this study. This led to some concern around whether this was the result of a higher incidence of ARIA events in homozygotes and functional unblinding. A number of additional analyses were conducted to address this concern that were reassuring, and this issue was considered resolved.

<u>Key secondary endpoints</u>

- Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels.

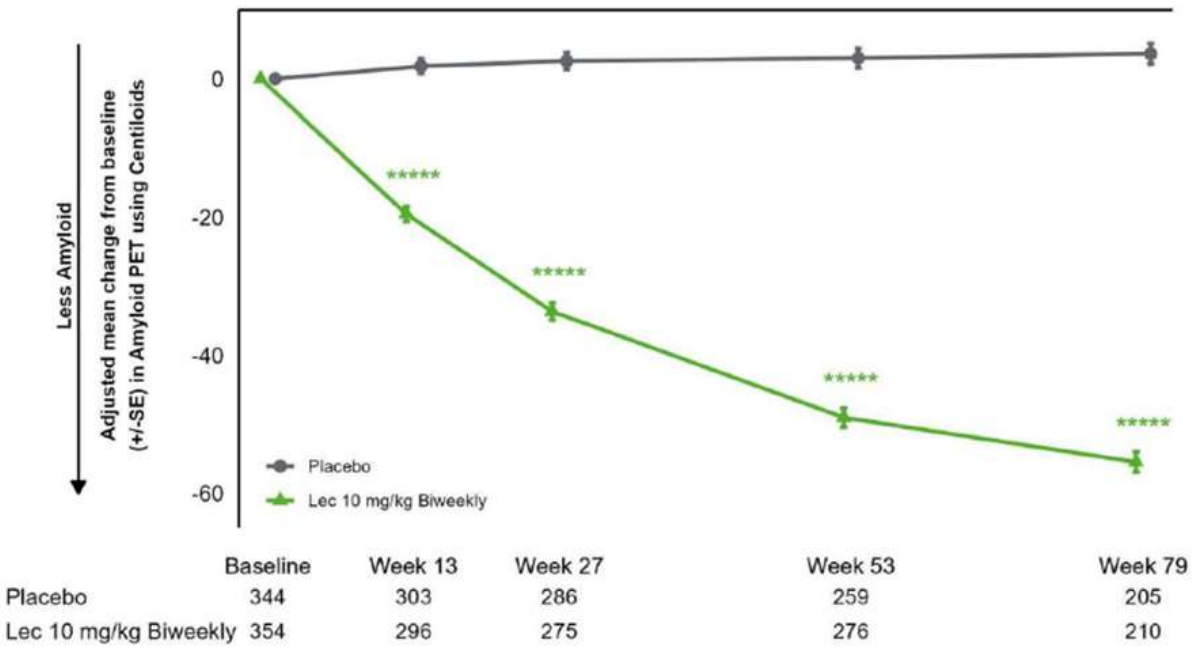
Centiloid values are presented by combining data across all tracers. The extent of amyloid reduction is dependent on baseline amyloid levels.

Table CE23: Change from baseline in Amyloid PET at 18 months – MMRM – Core study – PD analysis set (amyloid PET)*

Parameter Visit Statistic	Placebo (N = 353)	Lecanemab 10 mg/kg Biweekly (N = 363)
Amyloid PET using Centiloids		
Baseline		
n	351	360
Mean(SD)	75.026 (41.8240)	77.918 (44.8389)
Median	78.917	82.127
Min, Max	-16.98, 179.59	-16.55, 213.21
Amyloid PET using Centiloids		
Week 79		
m	344	354
n	205	210
Adjusted mean (SE)	3.637 (1.470)	-55.481 (1.457)
Adjusted mean difference: Lecanemab - Placebo		-59.118
95% Confidence interval for differences		-62.640, -55.596
P-value		<.00001

* Table adapted from tables 14.2.2.1.1 and 14.2.2.1.2 in the CSR

Figure CE8: Plot of adjusted mean (+/-SE) of change from baseline in amyloid PET using Centiloids for brain amyloid levels – Core study (PD analysis set)



Forty percent of subjects were included in the amyloid PET substudy (353 in the placebo group and 363 in the lecanemab group). A clear reduction in PET amyloid was observed with lecanemab at month 18 compared with placebo, where a slight increase was observed. At baseline, mean amyloid PET using centiloids was similar in the placebo (75.0) and lecanemab (77.9) group. At 18 months the mean in the lecanemab group had decreased to 23.0 which is below the threshold for amyloid negativity of approximately 30 centiloids.

The decrease in amyloid PET with lecanemab treatment shows a time dependent response. A rapid decline is seen up to week 53, after which the decline slows. Based on an exploratory endpoint analysis, at 18 months 60.4% of subjects in the lecanemab group had converted from amyloid positive to negative by centiloids compared with 0.6% in the placebo group.

- Change from baseline in ADAS-Cog14 at 18 months.

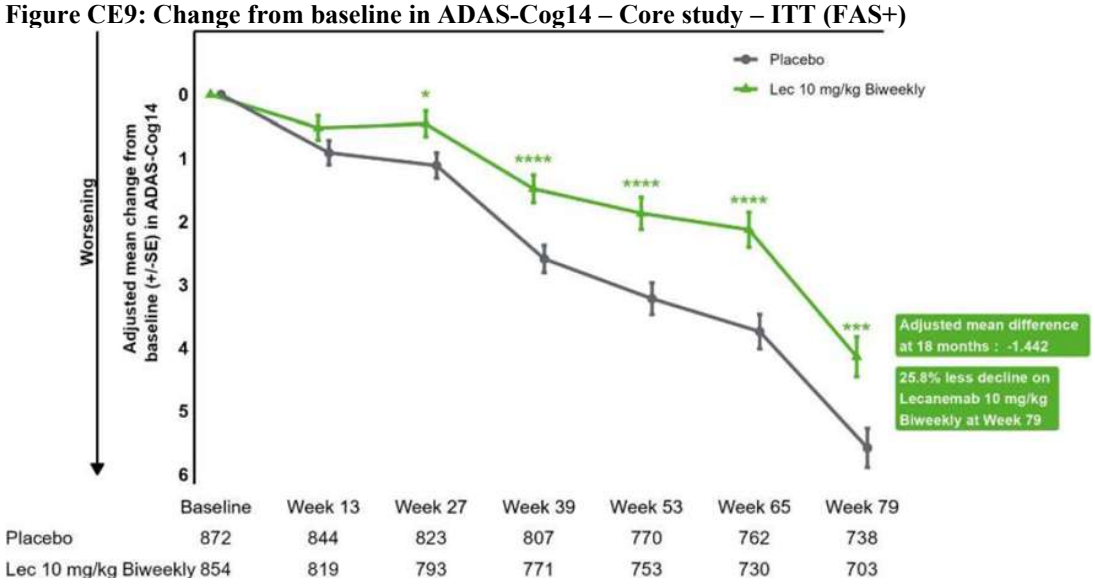
Table CE24: Summary of change from baseline in ADAS-Cog14 at 18 months – Core study – ITT (FAS+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADAS-Cog14		
Week 79		
n	740	705
Mean (SD)	28.55 (11.873)	28.00 (10.858)
Median	28.00	28.00
Min, Max	1.3, 90.0	2.0, 86.0
Change from Baseline		
n	738	703
Mean (SD)	4.61 (8.305)	3.80 (7.783)
Median	3.66	3.33
Min, Max	-14.0, 47.3	-26.7, 40.0

Table CE25: Statistical analysis of change from baseline in ADAS-Cog14 at 18 months – MMRM Core study – ITT (FAS+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADAS-Cog14		
Week 79		
m	872	854
n	738	703
Adjusted mean (SE)	5.581 (0.309)	4.140 (0.314)
Adjusted mean difference: Lecanemab - Placebo		-1.442
95% Confidence interval for differences		-2.270, -0.613
P-value		0.00065
% Difference vs. Placebo		-25.8%

Figure CE9: Change from baseline in ADAS-Cog14 – Core study – ITT (FAS+)



- Change from baseline in ADCOMS at 18 months.

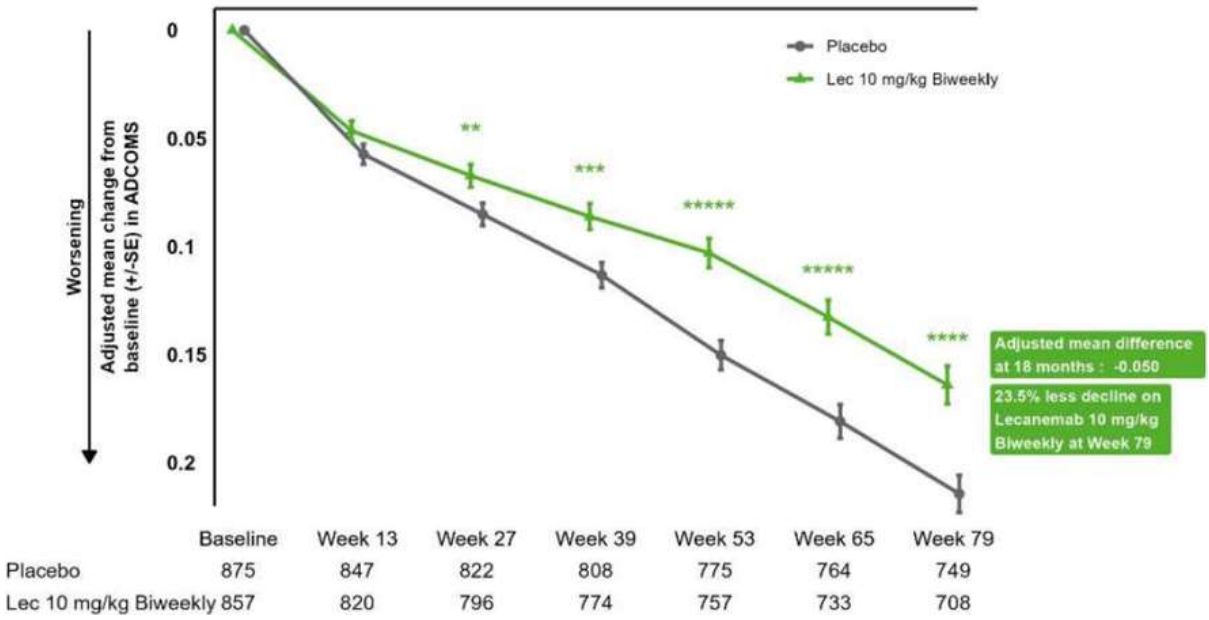
Table CE26: Summary of change from baseline in ADCOMS at 18 months – Core study – ITT (FAS+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADCOMS		
Week 79		
n	749	708
Mean (SD)	0.589 (0.3036)	0.541 (0.2784)
Median	0.530	0.485
Min, Max	0.00, 1.92	0.05, 1.57
Change from Baseline		
n	749	708
Mean (SD)	0.199 (0.2463)	0.152 (0.2213)
Median	0.144	0.110
Min, Max	-0.32, 1.39	-0.24, 1.18

Table CE27: Statistical analysis of change from baseline in ADCOMS at 18 months – MMRM Core study – ITT (FAS+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADCOMS		
Week 79		
m	875	857
n	749	708
Adjusted mean (SE)	0.214 (0.009)	0.164 (0.009)
Adjusted mean difference: Lecanemab - Placebo		-0.050
95% Confidence interval for differences		-0.074, -0.027
P-value		0.00002
% Difference vs. Placebo		-23.5%

Figure CE10: Change from baseline in ADCOMS – Core study ITT (FAS+)



- Change from baseline in ADCS MCI-ADL at 18 months.

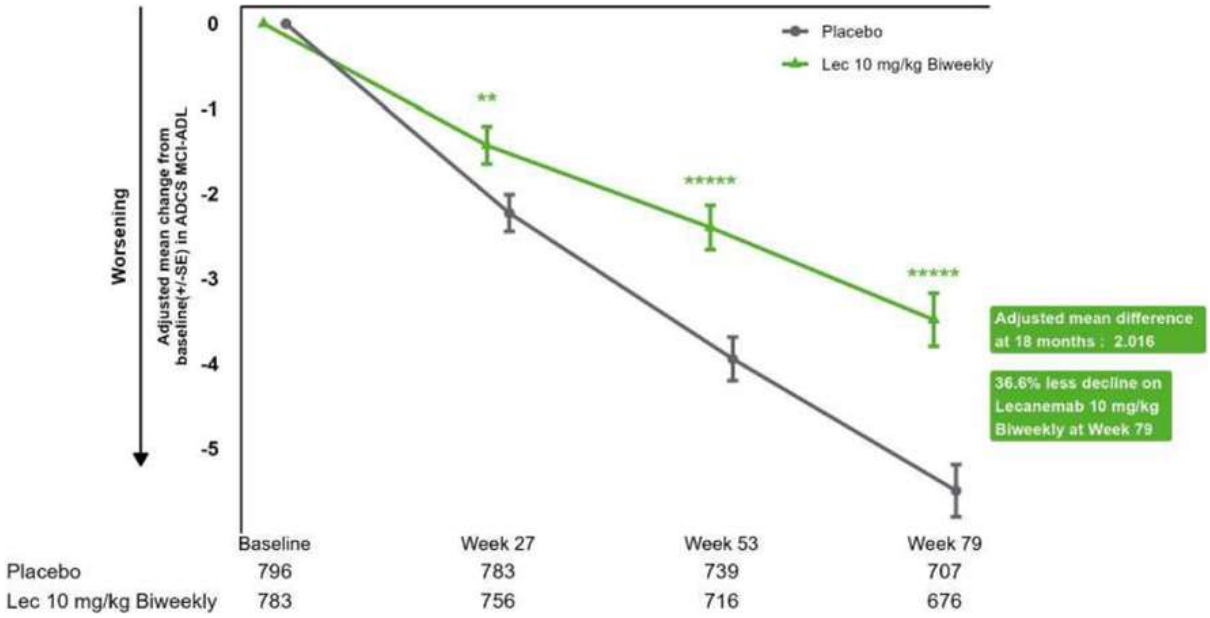
Table CE28: Summary of change from baseline in ADCS MCI-ADL at 18 months – Core study – ITT (FAS+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADCS MCI-ADL		
Week 79		
n	754	715
Mean(SD)	36.9 (10.03)	38.4 (9.13)
Median	39.0	40.0
Min, Max	1, 53	4, 53
Change from Baseline		
n	707	676
Mean(SD)	-4.5 (8.40)	-2.8 (7.46)
Median	-3.0	-2.0
Min, Max	-42, 19	-39, 20

Table CE29: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM Core study – ITT (FAS+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADCS MCI-ADL		
Week 79		
m	796	783
n	707	676
Adjusted mean (SE)	-5.500 (0.308)	-3.484 (0.313)
Adjusted mean difference: Lecanemab - Placebo		2.016
95% Confidence interval for differences		1.208, 2.823
P-value		<.00001
% Difference vs. Placebo		-36.6%

Figure CE11: Change from baseline in ADCS MCI-ADL – Core study ITT (FAS+)



Statistically significant results favouring lecanemab were observed for all 3 secondary clinical endpoints. Whilst a decline was seen in both groups, lecanemab resulted in a reduction in change from baseline as measured on the ADAS-Cog 14 (-1.442 [-26%], p=0.00065), ADCOMS (-0.050 [-24%], p=0.00002) and ADCS-ADL-MCI (2.016 [-37%], p<0.00001) as compared to placebo. Overall results in the sensitivity analyses are consistent

with the primary analyses.

As with the primary endpoint, there was differential ascertainment of ADAS-Cog14, ADCOMS, and ADCS MCI-ADL for the placebo and LEC10-BW arms, with missing data at 79 weeks greater in the latter. As described above for the primary endpoint, the applicant, therefore, repeated key secondary analyses using all randomised subjects and control-based multiple imputation in an MMRM analysis and using an ANCOVA. The results on re-analysis were similar to the main analysis.

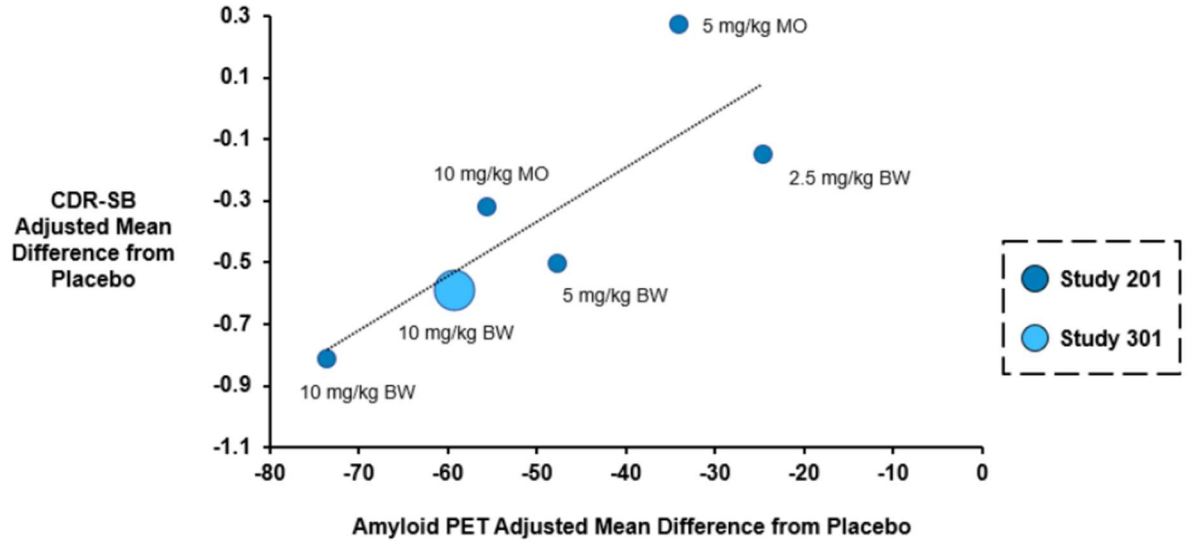
Selected biomarker endpoints

- Correlation between clinical changes and changes in amyloid PET

Population level correlations were calculated using adjusted mean difference from placebo between amyloid PET (Centiloids) and clinical endpoints, which are estimated using the MMRM used for main analysis in Study 201 and study 301 based on the subjects who have both amyloid PET (Centiloids) and clinical endpoint data at 12 months and/or 18 months.

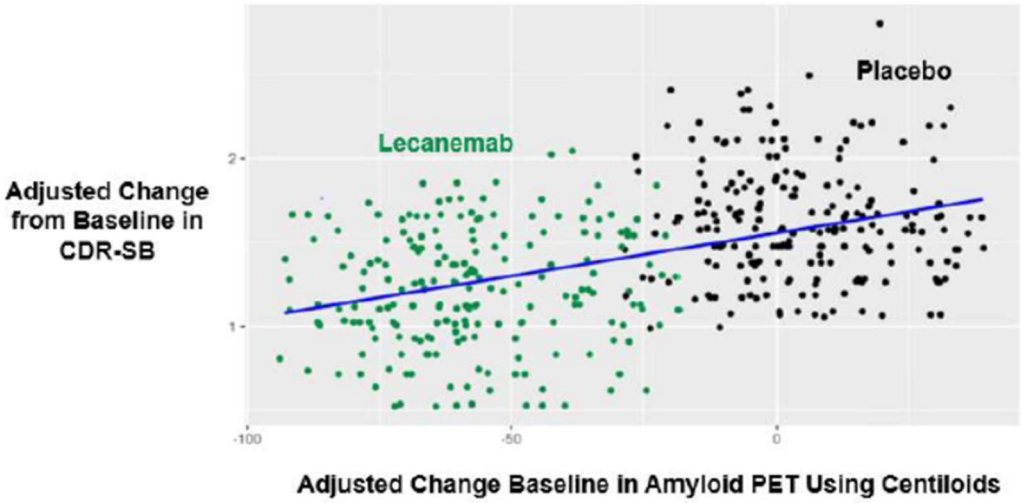
The population level correlation across lecanemab studies and different doses, demonstrates a relationship between reduction in amyloid PET (Centiloids) and clinical decline on CDR-SB (Pearson correlation coefficient=0.82, P=0.0463). This population level correlation demonstrates that the net effect of LEC10-BW on the biomarker is correlated with the net effect of the treatment on the clinical endpoint.

Figure CE12: Group-level correlation-relationship between reduction in amyloid PET (SUVR) and CDR-SB at 18 months



There is a patient-level correlation between the amount of amyloid removal as measured on amyloid PET (Centiloids) and CDR-SB (Figure CE13, Pearson correlation coefficient=0.45, P<0.0001), based on primary analysis model.

Figure CE13: Linear Trend Between Reduction in Amyloid PET (Centiloids) and Slowing On CDR-SB – Study 301 Core



Mediation analyses conducted using Prentice Criteria 1, 2, and 4 suggest that LEC10-BW treatment effect on CDR-SB is related to the treatment effect on brain amyloid reduction. Mediation analyses were conducted to explore the link between the effect of LEC10-BW on CDR-SB, and on brain amyloid load, as measured by amyloid PET (Centiloids). Eighty percent (80%) of the effect on CDR-SB can be explained by reduction in amyloid PET (Centiloids).

Table CE30: Mediation Analysis Between Change in CDR-SB and Change in Amyloid PET at 18 Months – Study 301 Core

Biomarker: Amyloid PET using Centiloids at 18 months	**CDR-SB**
Number of subjects in the analysis (PBO, LEC10-BW)	204, 203
Treatment effect on the biomarker	
Adjusted mean difference from PBO (SE)	-59.56 (2.078)
p-value (compared to PBO)[a]	<0.00001
Treatment effect on the clinical endpoint **without** adjusting for the biomarker	
Adjusted mean difference from PBO (SE)	-0.429 (0.189)
p-value (compared to PBO)[b]	0.02373
Treatment effect on the clinical endpoint **with** adjusting for the biomarker	
Adjusted mean difference from PBO (SE)	-0.086 (0.331)
p-value (compared to PBO) [c]	0.79516
Proportion of treatment effect on clinical endpoint explained by the biomarker (PTE)	80.0%

BW = biweekly, CDR-SB = Clinical Dementia Rating-Sum of Boxes, LEC10-BW = lecanemab 10 mg/kg IV biweekly, PBO = placebo, PET = positron emission tomography, PTE = proportion of treatment effect, SE = standard error.
A Prentice criteria 1 satisfied: Treatment is significant on surrogate endpoint (PET CL).
B Prentice criteria 2 satisfied: Treatment is significant on true endpoint (CDR-SB)
c Prentice criteria 4 satisfied: Treatment becomes not significant on true endpoint (CDR-SB) if surrogate endpoint (PET CL) is included in the model

This data provides some reassurance of a link between amyloid PET and clinical efficacy endpoints.

- Change from baseline in Tau PET Signal

Two hundred and fifty-seven subjects were included in the Tau PET substudy (placebo 122, lecanemab 135). There was a statistically significant change from baseline in brain tau pathology in 3 composite regions known to accumulate tau early in the disease (i.e., temporal, medial temporal, and meta-temporal) as measured by tau PET SUVR at 18 months with lecanemab compared to placebo (medial temporal ROI: adjusted mean treatment difference -0.068, P=0.00237; meta-temporal ROI: -0.071, P=0.01195; temporal ROI: adjusted mean treatment difference -0.065, P=0.01619). These temporal regions had the highest tau PET SUVR levels at baseline compared to other brain regions in both groups.

No statistically significant effects were observed at 18 months on the global tau load and on the change from baseline in occipital, parietal, cingulate, and frontal regions and in the whole cortical gray matter.

- vMRI

At 18 months of treatment, lecanemab demonstrated a statistically significant slowing of total hippocampal atrophy. Compared to placebo, lecanemab resulted in greater reductions in whole brain volume and cortical thickness with ventricular enlargement on lecanemab compared with placebo.

Table CE31: Summary of vMRI analysis – PD analysis set 1

Baseline (m^3)			**LS Mean Change from baseline (week 79)**		
Region	**Lecanemab (n=805)**	**Placebo (n=825)**	**Lecanemab (n=643)**	**Placebo (n=667)**	**Difference from placebo (95% CI)**
Hippocampal	6594	6681	-189	-208	19 (2, 32)
Whole brain	999663	1009173	-21819	-17742	-4077 (-5123, -3030)
Lateral ventricular	44193	43521	7302	5521	1781 (1397, 2164)
Cortical thickness (mm)	2.601	2.608	-0.134	-0.116	-0.018 (-0.025, -0.012)

The effects of accelerated brain volume loss on cognition associated with lecanemab treatment for up to 18 months were explored. Correlation analyses evaluated the relationships between brain volume loss and clinical outcomes, extent of amyloid removal and plasma biomarkers for whole brain, cortical thickness, lateral ventricular and hippocampal volumes.

Forest plots showed greater lateral ventricular volume loss in those experiencing ARIAs following lecanemab treatment than in those without ARIAs, however there was no effect of ARIA on cortical thickness or hippocampal volume. At an individual level in the placebo arm of the study, decreases from baseline in whole brain volume and increases in ventricular volume are correlated with decline in clinical endpoints. However, the observed changes in brain volume following 18 months of lecanemab treatment were not associated with adverse cognitive outcomes or increasing disease biomarkers consistent with accelerated neurodegeneration. The observed changes in brain volumes in those receiving lecanemab

follow amyloid plaque clearance but other potential causes have been proposed, including reduced inflammation (pseudoatrophy), fluid shifts and neuronal loss. Longer-term volumetric data will be required to characterise the risk of accelerated brain volume loss as the underlying cause(s) have not yet been fully elucidated.

The safety concern 'accelerated brain volume loss' has been included as missing information in the RMP. The Applicant will provide longer-term brain volume data from study 303 which will compare the brain volumes of patients with preclinical AD receiving lecanemab for up to 4 years against those receiving placebo.

A description of the available data on changes in brain volumes has been added to section 5.1 of the summary of product characteristics to inform healthcare professionals of this safety concern.

- CSF Fluid Biomarkers

Lecanemab demonstrated a statistically significant increase compared to placebo at 18 months for CSF Aβ(1-42) and a statistically significant decrease compared to placebo at 18 months for CSF p-tau181, CSF t-tau and CSF neurogranin.

Exploratory endpoints

- Quality of life

There was a statistically significant difference between placebo and lecanemab on change from baseline in EQ-5D-5L Health today by subject at 18 months in the subject's survey: adjusted mean treatment difference of 2.017, and 49.1% less decline, P=0.00383. Change from baseline in EQ-5D-5L health status did not have a statistically significant difference between placebo and lecanemab in the partner as a proxy survey or partner's survey.

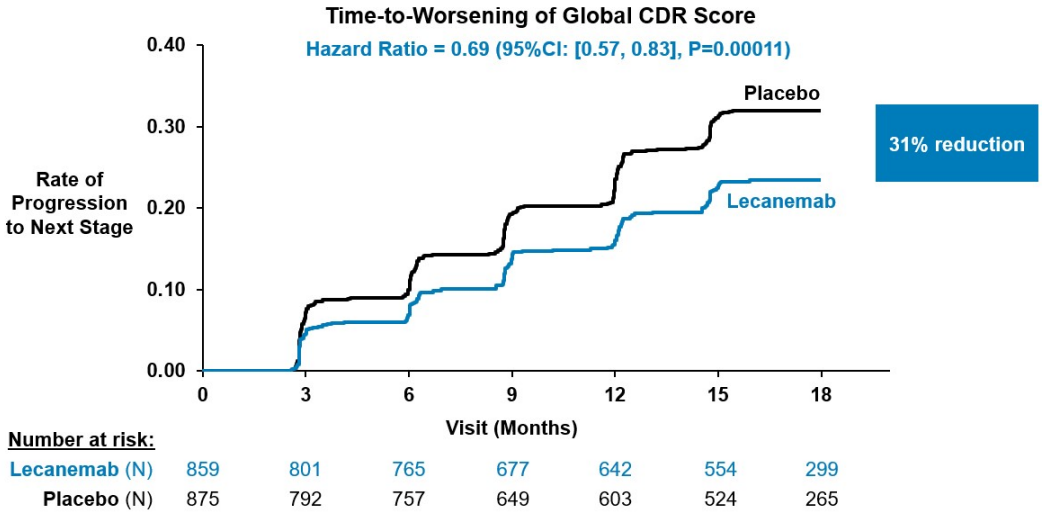
There was a statistically significant difference between placebo and lecanemab on change from baseline for QOL-AD total score in the subject's survey (adjusted mean treatment difference of 0.657, and 55.6% less decline, P=0.00231) and in the partner as a proxy survey (adjusted mean treatment difference of 0.535, and 22.9% less decline, P=0.02558).

There was a statistically significant difference between placebo and lecanemab on change from baseline for Zarit Burden Interview (ZBI) of Study Partner score (adjusted mean treatment difference of -2.211, and 38.4% less decline, P=0.00002).

- Time to worsening of global Clinical Dementia Rating (CDR) score by 18 months

Time to worsening of a global CDR score was defined as time from randomization to the time of worsening of the global CDR score (i.e., the 1st worsening where there is an increase from Baseline by at least 0.5 points for MCI subjects and by at least 1 point for mild AD subjects on the global CDR score in 2 consecutive visits)

Figure CE14: Kaplan–Meier Curves for Time to Worsening of Global CDR Score – Study 301 Core (ITT FAS+)



Lecanemab reduced the risk of progression to the next stage of AD on the global CDR score at 18 months by 31% compared with placebo (hazard ratio 0.69; 95% CI 0.572 to 0.833). The proportion of subjects who experienced worsening of Global CDR ≥ 0.5 was 29.9% in the placebo arm vs 21.7% in the lecanemab arm. On repeating the analysis of the time to worsening of Global CDR by at least 0.5 points among the subgroup with a CDR Global score of 0.5, the hazard ratio was similar to the main analysis in the whole population.

Ancillary analyses

Subgroup analyses

- CDR-SB

Figure CE15: Lecanemab vs placebo by randomisation strata – Core study – ITT (FAS+)

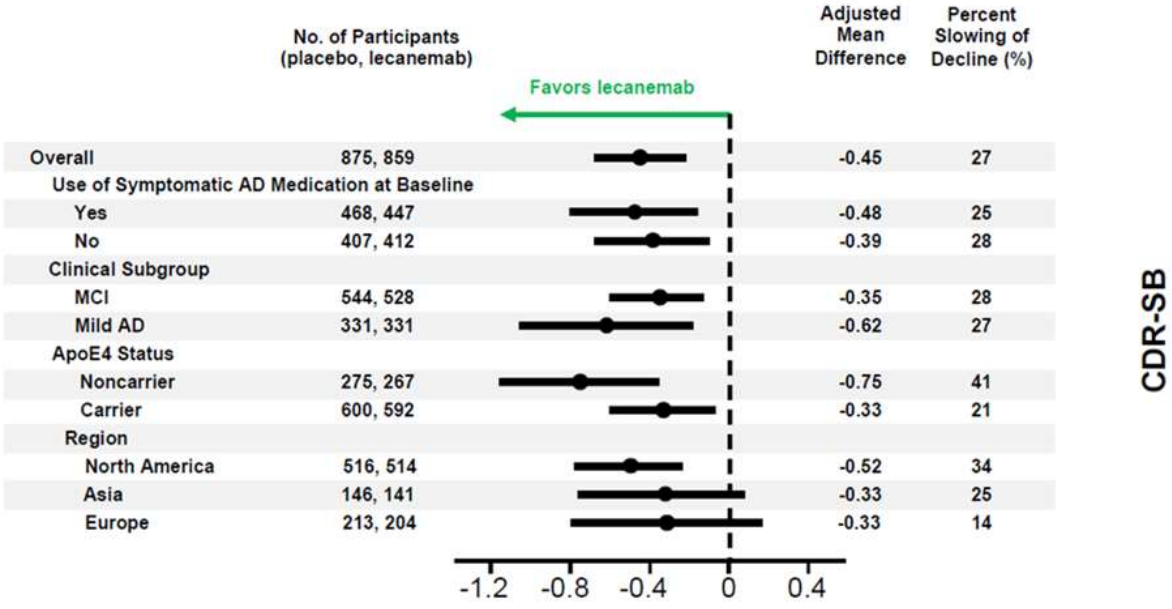
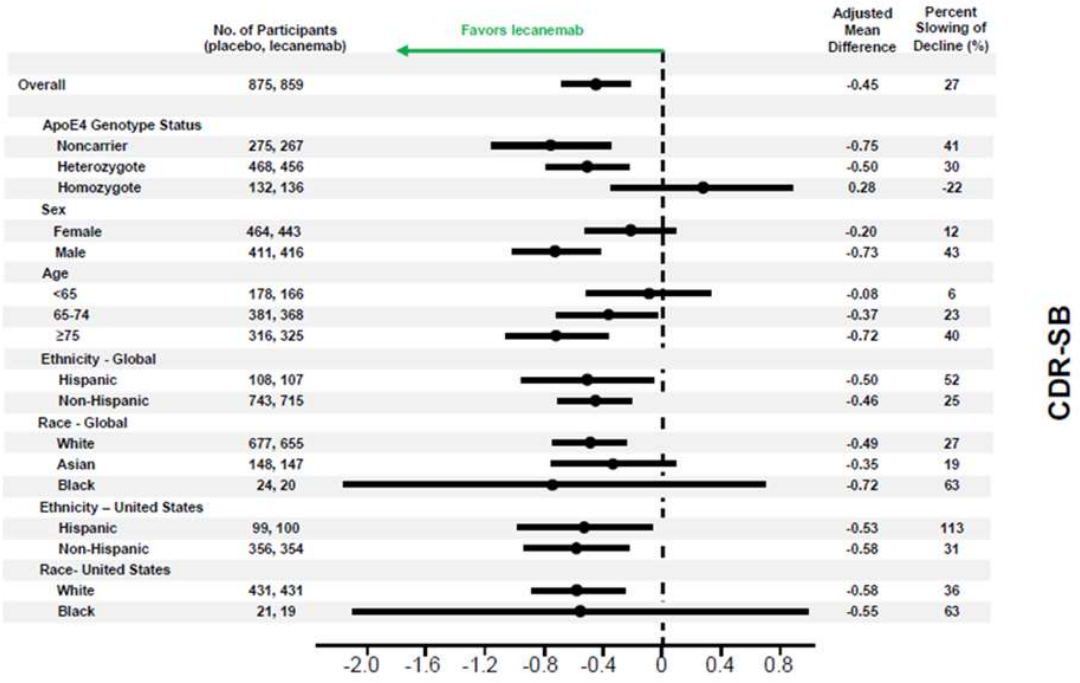
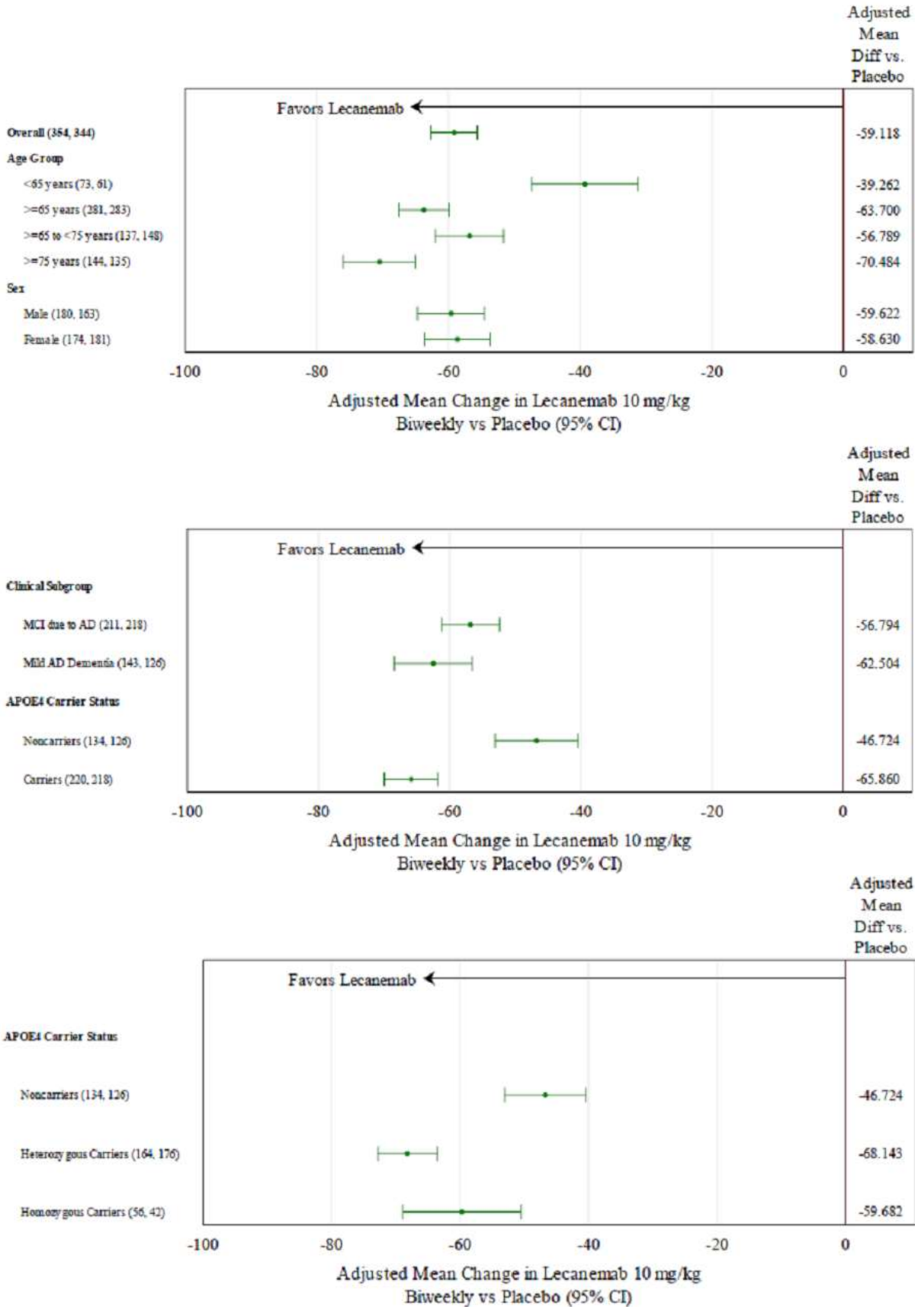


Figure CE16: Lecanemab vs placebo by intrinsic factors



- Amyloid PET

Figure CE17: Forest Plot of change from baseline in Amyloid PET using Centiloids at 18 Months Core Study PD Analysis Set (Amyloid PET) by age group, sex, clinical subgroup and ApoE4 Carrier Status – Core Study – PD Analysis Set (Amyloid PET)

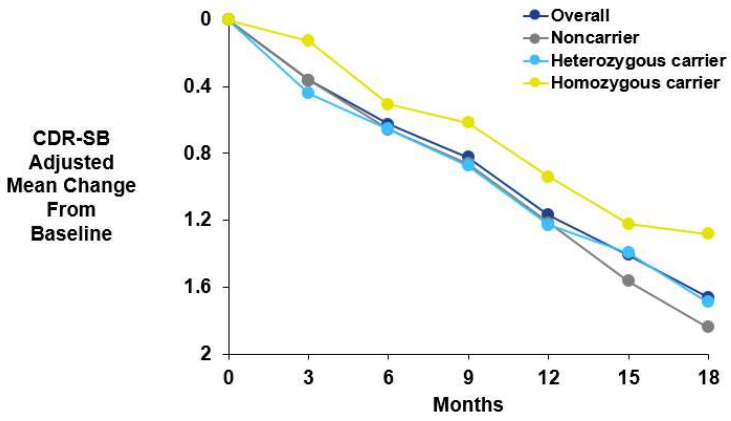


Prespecified subgroup analyses performed across randomisation strata and intrinsic factors for the primary endpoint, change in baseline in CDR-SB, favoured lecanemab except for in ApoE4 homozygous subjects.

ApoE4 carrier status (carrier/noncarrier) was a stratification factor in study 301. Whilst still favouring lecanemab treatment over placebo, the size effect in ApoE4 carriers was smaller than that in non-carriers. This is opposite to the findings in study 201.

ApoE4 homozygotes were one of the smallest pre-specified subgroups (15%) in the overall population. Whilst ApoE4 genotype (as opposed to carrier status) was not a stratification factor, the number of ApoE4 homozygotes was balanced in the lecanemab and placebo groups. The discrepant results in homozygous patients on CDR-SB may in part be explained by the unexpectedly slower decline seen in the homozygous ApoE4 homozygous subjects in the placebo group in study 301:

Figure CE18: Change From Baseline in CDR-SB in Study 301 Core – Overall and by Genotype



Results for the validated secondary endpoints ADAS-Cog14 and ADCS ADL-MCI in homozygous patients favour lecanemab, although the effect size is less than in heterozygous and non-carriers, and the results for Quality-of-Life measures and biomarkers (amyloid PET, CSF p-tau181 and CSF neurogranin) are consistent with the overall population.

Based on the available data, a benefit of lecanemab in ApoE4 homozygous patients cannot be excluded. However, there is a greater uncertainty around the magnitude of benefit in this subgroup of patients.

A greater effect size on CDR-SB was seen with increasing age. Subjects aged <65 years represented a smaller group compared with those aged ≥ 65 to <75 years or ≥ 75 years. For all clinical endpoints, and for the majority of biomarker and QoL endpoints, the point estimate for subjects <65 years favoured lecanemab. Statistical interaction tests do not suggest that the treatment effect differs across subgroups for age. The totality of the clinical data supports use in patients <65 years.

Although the change on amyloid PET was similar for male and female subjects, the data suggest that the effect size for the CDR-SB endpoint may be lower in females than in males.

For all clinical, biomarker and QoL endpoints, the point estimate for female subjects favoured lecanemab. Statistical interaction tests do not suggest that the treatment effect differs by sex except for the effect on ADCS MCI-ADL which showed weak evidence of an interaction by sex (p=0.06). However, the point estimate for females in the forest plot for ADCS MCI-ADL is comfortably in favour of lecanemab. The totality of the clinical data supports use in female patients.

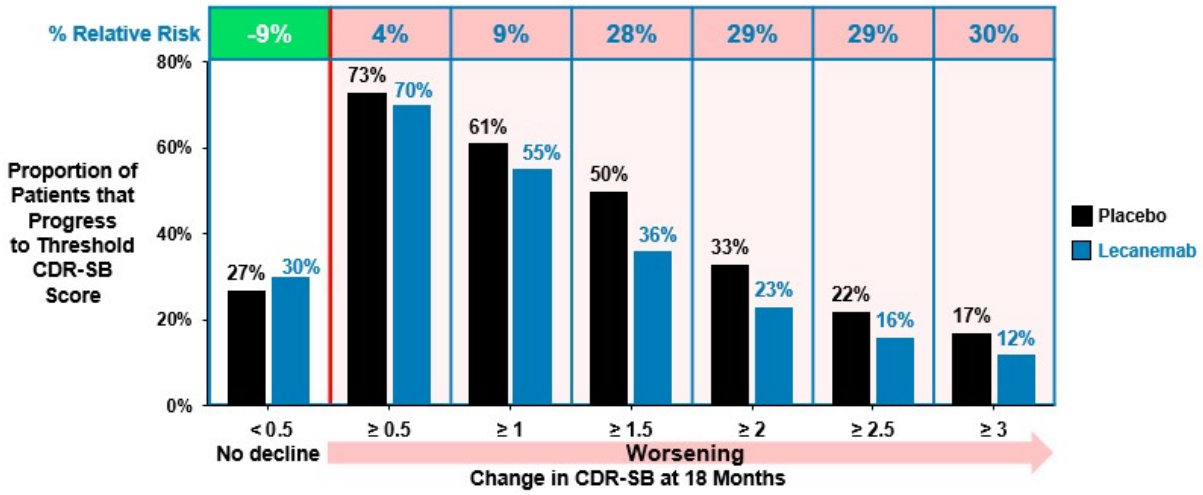
Except for the results in homozygous subjects discussed above, the subgroup analyses for the other clinical endpoints (ADAS-Cog14, ADCOMS and ADCS MCI-ADL) were generally consistent with the CDR-SB subgroup analyses.

Progressor analyses

Responder and time to event analyses can be used to establish the clinical relevance of the treatment effect after statistical significance has been established on the mean level of the required primary variables. Time to worsening of global CDR score by 18 months was an exploratory endpoint and the results are described above.

To further contextualise the clinical meaningfulness of the efficacy results, a progressor analysis to assess the proportion of subjects in placebo (PBO) and LEC10-BW that progressed by increasing thresholds on the CDR-SB scale in Study 301 at 18 months was provided.

Figure CE19: Proportion of Subjects with Cognitive and/or Functional Worsening on CDR-SB at 18 Months - Study 301 Core (Randomised Set)



ITT population, missing data handled through control-based imputation

Fewer LEC10-BW subjects declined compared to PBO, regardless of the threshold applied from 0.5 to a 3-point worsening.

Similarly, for ADAS-Cog14 and ADCS MCI-ADL scales at 18 months, fewer LEC10-BW subjects declined compared to PBO, regardless of the threshold applied.

Supportive studies

The development program of lecanemab includes one open-label extension of the Phase 2 study (Study 201 OLE) and one open-label extension of the Phase 3 study (Study 301 OLE).

Study 201 OLE

Any subject who completed Visit 42 (Week 79) of the Core Study 201 had the option to participate in the OLE Phase. Subjects who previously completed the Core Study (through the Follow-Up Visit [Week 90]) and/or fulfilled the OLE Phase inclusion and exclusion criteria were eligible to participate. Subjects who discontinued the Core Study were eligible to participate in the OLE Phase, provided they met the inclusion and exclusion criteria for the OLE Phase.

The OLE was initiated after analysis of the Core Study was complete and clinical study report (CSR) finalised, resulting in an average 24-month (range 9-59 months) Gap Period off study drug between the final visit in the Core Study (Week 79) and OLE Baseline Visit.

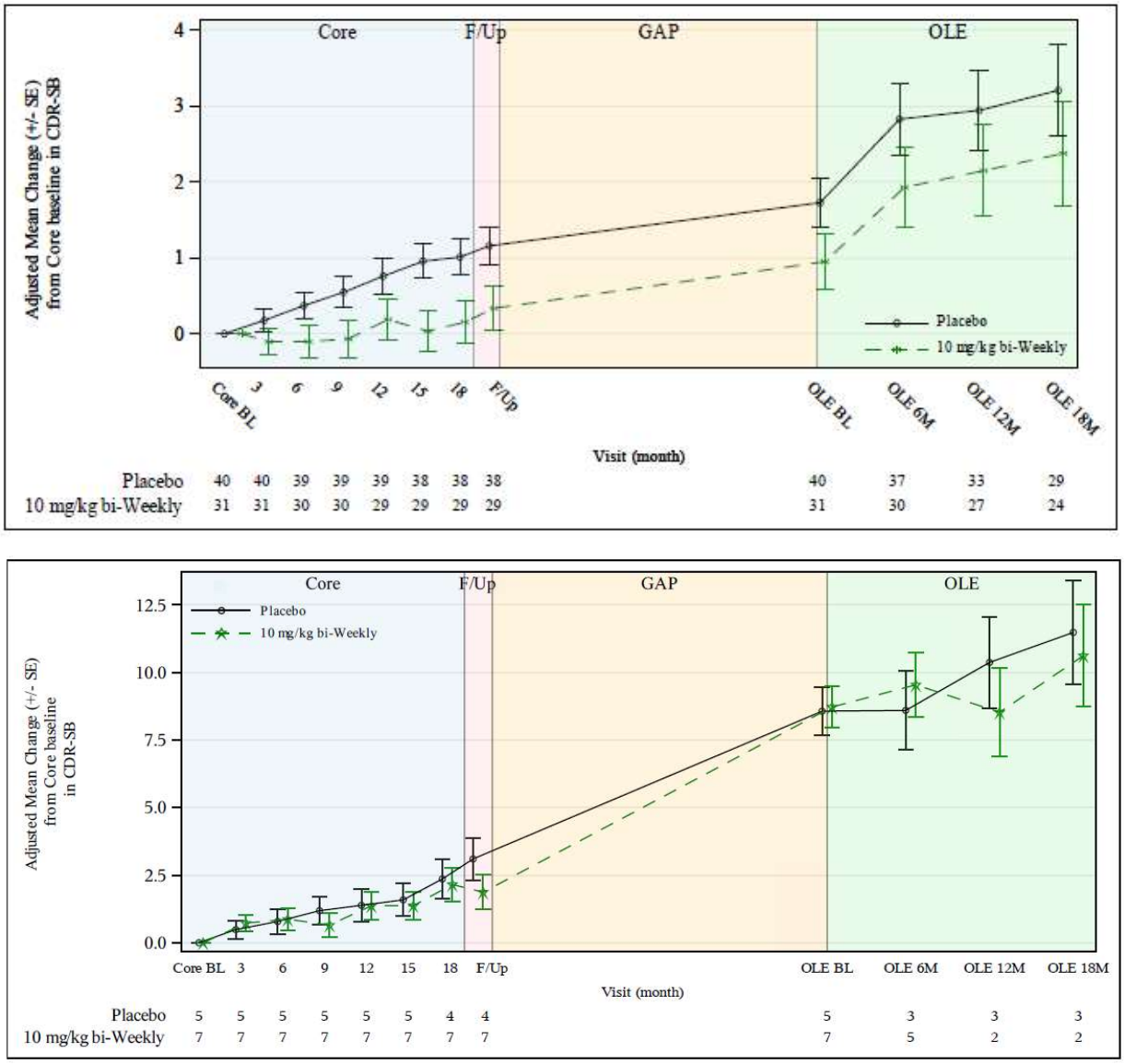
Of the 180 subjects that received lecanemab 10mg/kg biweekly in the OLE phase; 45 were newly treated having received placebo in the core study, 37 were re-treated having received low doses in the core study, 60 were re-treated having received 10mg/kg monthly in the core study and 38 were re-treated having received 10mg/kg biweekly in the core study.

The 2 main groups of interest are the ‘Newly treated core Placebo’ and ‘Re-treated Core 10mg/kg biweekly’. The summary statistics for the gap duration for these 2 groups are reasonably similar.

At OLE baseline, 150 subjects continued to have early AD with a global CDR of ≤1 and 30 had progressed beyond EAD (28 with moderate AD and 2 with severe AD).

As of the data cutoff date, 98 (54.4%) subjects were ongoing in the OLE Phase. The most common primary reasons for discontinuation from the OLE phase of the study were subject choice (30 [16.7%] subjects) and withdrawal of consent (24 [13.3%] subjects). Eight (4.4%) out of the total of 180 subjects discontinued the study due to AEs.

Figure CE20: Adjusted Mean Change From Core Baseline in CDR-SB – Study 201 Core, Gap and OLE Period (OLE Enrolled Set), Global CDR Group ≤1, Top Figure; Global CDR Group >1, Bottom Figure)



Due to the optional and uncontrolled nature of the 201 OLE, the relatively small number of subjects enrolled across the different core treatment groups, the significant range in the gap period off study drug (9-59 months) and the number of subjects that discontinued the OLE up to the data-cut off, the interpretation and conclusions that can be drawn from this data are limited.

However, the data in subjects with a global CDR ≤ 1 at the OLE baseline does appear to suggest the separation between the placebo and treated group (10mg/kg biweekly) for CDR-SB is maintained during the gap period providing some support for a disease modifying effect of treatment. The data in subjects that had a global CDR >1 is difficult to interpret, given the small sample size per treatment group and different scale used in the figures provided. However, it is clear that the progression is much more rapid in these subjects and there appears to be no clear separation of the curves for CDR-SB between placebo and lecanemab 10mg/kg biweekly in the core period.

Study 301 OLE

Subjects who completed the 301 Core study could participate in the 301 OLE study which began at 18 months from Core baseline. At the start of the OLE study, subjects allocated to placebo in the Core study were switched to LEC10BW (the delayed-start group) while those allocated to LEC10BW continued treatment as before (the early-start group).

The applicant provided follow-up data to 24 months from the 301 Core study baseline (i.e. 6 months in the OLE study) and subsequently provided additional follow-up data to 30 months (i.e. 12 months in the OLE study) for CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL (see summary Table below).

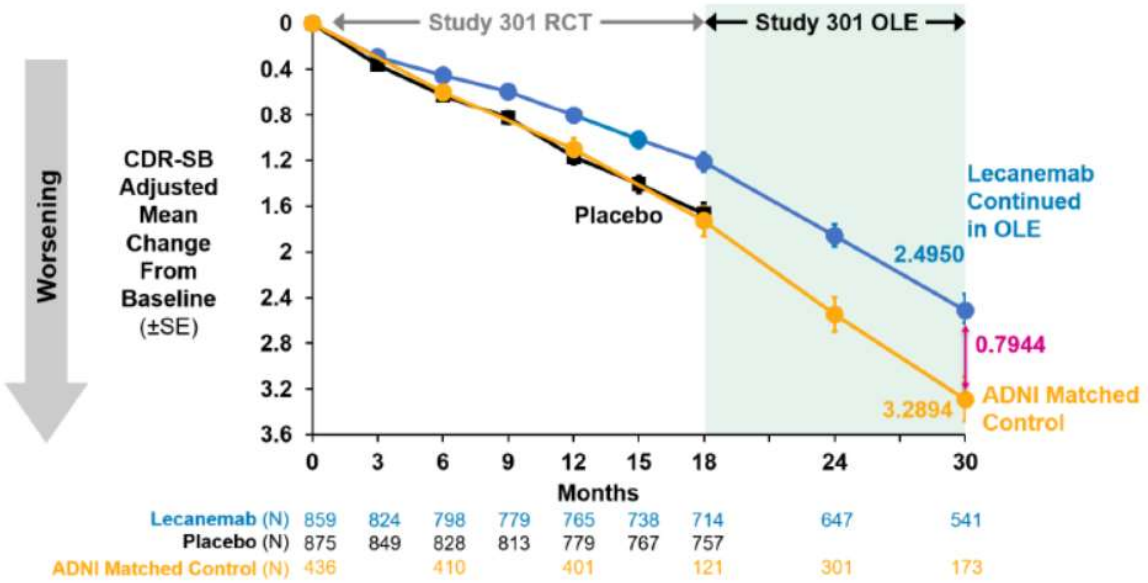
Table: Adjusted mean difference of change from baseline in clinical endpoints

Time from 301 Core Baseline	Adjusted mean difference (95% CI)		
	CDR-SB	ADAS-Cog14	ADCS-MCI-ADL
18 months (OLE Baseline)	-0.450 (-0.668 to -0.232)	-1.402 (-2.232 to -0.573)	1.997 (1.191 to 2.803)
24 months (OLE 6 months)	-0.360 (-0.628 to -0.091)	-1.352 (-2.344 to -0.361)	1.777 (0.833 to 2.722)
30 months (OLE 12 months)	-0.355 (-0.698 to -0.013)	-0.873 (-2.203 to 0.457)	1.630 (0.433 to 2.827)

Between the OLE baseline at 18 months and the end of follow-up at 30 months, data suggest a reduction in the treatment difference between delayed-start and early-start arms. While data suggest the treatment difference is not maintained in full throughout the OLE study period, the reduction observed for CDR-SB and ADCS-MCI-ADL appears modest and occurs over the period of a year. For both these endpoints, approximately 80% of the treatment effect observed at the start of the OLE period is observed a year later. While it is noted that the reduction in treatment difference was more marked for ADAS-Cog14, the data overall suggest a possible disease-modifying effect.

Data from an external (untreated with LEC10BW) observational cohort sourced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were selected to match with the 301 Core study population for the purpose of aiding interpretation of the uncontrolled open label extension data. Summary statistics for the baseline demographic and clinical characteristics of the ADNI cohort were reasonably similar to those of subjects in the 301 Core study at baseline. Whilst the applicant suggests that the treatment difference between the LEC10BW arm and the untreated ADNI cohort increases over time, the data provided to support this are limited. It was also noted that 61% (1066/1734) of subjects in the full analysis set at 301 Core study baseline were present at the 30-month time-point compared with 40% (173/436) of those in the ADNI cohort.

Figure CE21: Adjusted Mean Change (±SE) from Baseline in CDR-SB in Context of Observational Cohort through 30 months – Study 301 Core and OLE Phase (ITT FAS+)



Overall conclusions on clinical efficacy

The main dataset to support efficacy of lecanemab 10 mg/kg biweekly in the treatment of early Alzheimer's disease is from the single pivotal phase 3 study, 301 core. The study included a 60-day screening period, an 18-month placebo-controlled period, and a safety follow-up period of 3 months after the final dose.

Supportive efficacy data is provided from the 18-month placebo-controlled period of the phase 2 dose finding study, 201 and the uncontrolled open-label extension phases of study 201 and 301.

Lecanemab has a clear impact on amyloid beta plaque, reducing this in a dose and time-dependant manner.

The primary analyses of the primary and 2 key validated secondary efficacy endpoints for the pivotal clinical trial 301 core demonstrated statistically significant differences between lecanemab and placebo at 18 months:

- CDR-SB: -0.451 (95% CI: -0.669, -0.233; p=0.00005)
- ADAS-Cog14: -1.442 (95%CI: -2.270, -0.613; p=0.00065)
- ADCS MCI-ADL: 2.016 (95%CI: 1.208, 2.823; p<0.00001)

These are established efficacy endpoints covering a range of cognitive and functional aspects. When considering the individual domains/items that comprise the CDR-SB, ADAS-Cog14 and ADCS MCI-ADL, overall, a consistent effect was seen.

However, whilst these efficacy results are statistically significant, the absolute differences seen in the clinical efficacy endpoint scores between the placebo and lecanemab groups at 18-months were small, and patients continued to decline even on treatment, raising a question on whether the efficacy results are clinically meaningful.

To help contextualise the efficacy results, the typical scores for subjects with early AD and the rate of progression in the placebo group were taken into consideration. For the primary

endpoint CDR-SB, patients with EAD typically score in the range of 0.5 to 6 on the CDR-SB, and the natural disease progression in subjects with EAD is, at most, an average of 2 points on CDR-SB over 18 months. In study 301 core, the mean score at baseline was 3.20, the rate of progression in placebo subjects was 1.66 compared with 1.21 in the lecanemab group. This reflected an adjusted mean treatment difference of -0.451 (95% CI, -0.669 to -0.233).

Measuring group-level differences in study outcomes is considered the correct statistical approach to estimate treatment effects in parallel-group AD trials. However, complementary data analyses that estimate within-individual change may help contextualise the clinical meaningfulness of the between group differences seen, and were considered appropriate in this setting where statistical significance has been established on the mean level of the required primary and key secondary efficacy endpoints. Consequently, 'time-to-worsening' and 'progressor' analyses were presented.

Time to worsening of global CDR score was a prespecified exploratory endpoint in study 301 core. Lecanemab reduced the risk of progression to the next stage of AD on the global CDR score at 18 months by 31% compared with placebo (hazard ratio 0.69; 95% CI 0.572 to 0.833). The proportion of subjects who experienced worsening of Global CDR $\geq$ 0.5 was 29.9% in the placebo arm vs 21.7% in the lecanemab arm. Alzheimer's is a progressive disease, and moving at least 0.5 points on the global CDR score has a negative impact on patients and their carers.

In the progressor analyses provided, a smaller percentage of those on treatment experience worsening regardless of the cutoff point, favouring the treatment arm.

Progression of Alzheimer's disease is associated with worsening of quality of life and maintaining health-related quality of life has been identified as a clinically meaningful benefit by both the patients and their care partner(s). Lecanemab treatment was associated with a reduction in decline in the European Quality of Life–5 Dimensions 5 Level (EQ-5D-5L) version Health Today score by patient and Quality of Life in Alzheimer's disease total score by patient and care partner as proxy, and a reduction in the increase of the Zarit Burden Interview (a 22-item instrument to specifically assess the challenges experienced by care partners of individuals with AD) total score at 18 months compared to placebo. No treatment effect was seen for the EQ-5D-5L Health Today score by care partner or by care partner as proxy.

Pivotal clinical efficacy data are limited to the single phase 3 study 301 core. However, placebo-controlled efficacy data is also available from the phase 2 study 201 core. Whilst due to methodological issues, the results of study 201 core are considered exploratory, the clinical efficacy results in the overall population that received lecanemab 10mg/kg bi-weekly are consistent with those seen in study 301 core and provide some reassurance regarding replication of the results.

When taken in the context of the high burden Alzheimer's disease imposes on patients and their carers, the urgent high unmet medical need for effective treatments, and the benefits of reducing clinical decline, particularly at the early stage of disease when symptoms are still manageable and quality of life relatively preserved, it is considered that the efficacy results from the 18-month placebo-controlled period of study 301 in the overall population are clinically meaningful. However, whilst clinically meaningful, the overall benefits remain

modest and there are greater uncertainties around the magnitude of benefit in ApoE4 homozygous patients.

Whilst the totality of data, including from the gap period in study 201, delayed start data from the open label extension phase of study 301, 'time to worsening of global CDR analysis' and biomarker data, are considered to support a degree of disease modification in early Alzheimer's disease, the data are not considered robust enough to support a disease modifying indication at this time, particularly in terms of longer term outcomes. As such a treatment indication is considered more appropriate.

The duration of placebo-controlled data is limited to 18 months. The efficacy of continued treatment in patients with moderate Alzheimer's disease has not been established and treatment with lecanemab should be discontinued once the patient progresses to moderate Alzheimer's disease. This is highlighted in section 4.2 of the SmPC.

IV.5 Clinical safety

The main safety data presented are from studies 301 and 201. The data from Study 301 Core, Study 301 OLE, Study 201 Core and Study 201 OLE are presented individually.

Data presented for Study 301 OLE Phase are cumulative for any subject who received at least 1 dose of lecanemab 10mg/kg biweekly (LEC10-BW) at any time, whether in the Core or OLE Phase (data cut off 15 Apr 2022). Therefore, these data may be interpreted as a pooled presentation of all LEC10-BW treated subjects across the total duration of Study 301.

In addition, the following pooled analyses are presented:

- Pool Core: all subjects treated with at least 1 dose of study medication in Study 301 Core or Study 201 Core.
- Pool LEC10-BW: all subjects treated with LEC10-BW in Study 301 Core, Study 301 OLE, Study 201 Core, and Study 201 OLE.

Updated safety data was subsequently provided for study 201 OLE and study 301 OLE with a data cut-off 01 December 2022.

The LEC10 BW population in study 201 differs to that in study 301 because of the protocol amendments required whereby ApoE4 carriers could no longer be randomised to the 10mg/kg biweekly dose in study 201. Only 30% of LEC 10 BW subjects in study 201 core (safety analysis set; SAS) were ApoE4 carriers, compared with 69% in study 301 core (SAS). This needs to be taken into consideration when reviewing the data on amyloid related imaging abnormalities (ARIA) events as ApoE4 carriers, particularly homozygotes, have an increased risk of ARIA.

Patient exposure

Study 301

Table CS1: Cumulative extent of exposure – Study 301 Core (Safety analysis set)

Extent of Exposure	Placebo (N=897)	Lecanemab 10 mg/kg Biweekly (N=898)
Duration (months[a]), n (%)		
>0 weeks	897 (100.0)	898 (100.0)
≥6 weeks	890 (99.2)	867 (96.5)
≥3 months	874 (97.4)	834 (92.9)
≥6 months	857 (95.5)	811 (90.3)
≥9 months	810 (90.3)	782 (87.1)
≥12 months	797 (88.9)	757 (84.3)
≥15 months	772 (86.1)	728 (81.1)
≥18 months	549 (61.2)	513 (57.1)
Duration of exposure (months)		
n	897	898
Mean (SD)	16.49 (3.928)	15.74 (5.040)
Median	18.03	18.03
Min, Max	0.5, 20.0	0.5, 18.8
Total duration (subject-years)[b]	1232.99	1177.92

a: Duration (months) = ([date of last dose - date of first dose +1]/ 7 + 1 treatment cycle)/ 52*12, b: Total duration (subject-years = summation over all subjects' exposure durations

At the 15 April 2022 data cut-off, in Study 301 OLE Phase (LEC10-BW Treated Period) the mean duration of exposure to LEC10-BW for the 1391 ongoing subjects (898 treated with lecanemab in core study, 493 treated with lecanemab in OLE phase only) is 14.06 months, with 783 subjects exposed to LEC10-BW for at least 12 months and 221 subjects exposed to LEC10-BW for at least 24 months.

As of the data cut-off 01 December 2022, in the ongoing Study 301 OLE Phase, 1321 subjects were exposed to lecanemab for at least 6 months, with 505 subjects receiving lecanemab for at least 24 months. The mean duration of exposure in months for the 1612 subjects who participated in Study 301 Core and OLE Phase (all receiving LEC10-BW in the OLE Phase) is 17.35 months.

Study 201

Table CS2: Cumulative extent of exposure – Study 201 Core (SAS)

		Lecanemab					
Duration of Exposure	**Placebo (N=245)**	**2.5 mg/kg Biweekly (N=52)**	**5 mg/kg Monthly (N=51)**	**5 mg/kg Biweekly (N=92)**	**10 mg/kg Monthly (N=253)**	**10 mg/kg Biweekly (N=161)**	**Total (N=609)**
Duration (months)[a], n (%)							
≥6 weeks	240 (98.0)	51 (98.1)	50 (98.0)	90 (97.8)	243 (96.0)	151 (93.8)	585 (96.1)
≥3 months	229 (93.5)	48 (92.3)	48 (94.1)	84 (91.3)	225 (88.9)	124 (77.0)	529 (86.9)
≥6 months	222 (90.6)	46 (88.5)	47 (92.2)	83 (90.2)	201 (79.4)	106 (65.8)	483 (79.3)
≥9 months	210 (85.7)	44 (84.6)	46 (90.2)	76 (82.6)	187 (73.9)	100 (62.1)	453 (74.4)
≥12 months	202 (82.4)	41 (78.8)	45 (88.2)	75 (81.5)	175 (69.2)	97 (60.2)	433 (71.1)
≥15 months	193 (78.8)	38 (73.1)	42 (82.4)	72 (78.3)	167 (66.0)	91 (56.5)	410 (67.3)
≥18 months	157 (64.1)	30 (57.7)	40 (78.4)	57 (62.0)	160 (63.2)	76 (47.2)	363 (59.6)
Duration (months)							
n	245	52	51	92	253	161	609
Mean (SD)	15.62 (5.045)	15.09 (5.325)	16.52 (4.742)	15.28 (5.387)	14.02 (6.555)	12.10 (7.229)	14.00 (6.479)
Median	18.03	18.03	18.49	18.03	18.46	17.97	18.03
Min, Max	0.5, 19.2	1.1, 18.3	1.0, 18.9	1.0, 18.5	1.0, 19.0	0.5, 18.5	0.5, 19.0
Total duration (subject-years)[b]	319.00	65.37	70.21	117.15	295.50	162.29	710.52

a: Duration (months) = ([date of last dose - date of first dose +1]/ 7 + 1 treatment cycle)/52*12 b: Total duration (subject-years) = summation overall subject' s exposure durations

The slightly lower mean duration in the LEC10-BW treatment group is as a consequence of the protocol amendment required by Health Authorities in the European Union.

At the 15 April 2022 data cut-off, in Study 201 OLE Phase the mean duration of exposure to LEC10-BW for the 180 subjects is 26.09 months, with 149 subjects exposed to LEC10-BW for at least 12 months and 124 subjects exposed to LEC10-BW for at least 24 months.

As of the data cut-off of 01 December 2022, the number of patients exposed was unchanged. The mean duration of exposure to LEC10-BW for the 180 subjects was 30.13 months.

Pool Core

Table CS3: Cumulative extent of exposure – Pool Core (SAS)

		Lecanemab					
Duration of Exposure	Placebo (N=1142)	2.5 mg/kg Biweekly (N=52)	5 mg/kg Monthly (N=51)	5 mg/kg Biweekly (N=92)	10 mg/kg Monthly (N=253)	10 mg/kg Biweekly (N=1059)	Total (N=1507)
Duration (months)[a], n(%)							
≥6 weeks	1130 (98.9)	51 (98.1)	50 (98.0)	90 (97.8)	243 (96.0)	1018 (96.1)	1452 (96.4)
≥3 months	1103 (96.6)	48 (92.3)	48 (94.1)	84 (91.3)	225 (88.9)	958 (90.5)	1363 (90.4)
≥6 months	1079 (94.5)	46 (88.5)	47 (92.2)	83 (90.2)	201 (79.4)	917 (86.6)	1294 (85.9)
≥9 months	1020 (89.3)	44 (84.6)	46 (90.2)	76 (82.6)	187 (73.9)	882 (83.3)	1235 (82.0)
≥12 months	999 (87.5)	41 (78.8)	45 (88.2)	75 (81.5)	175 (69.2)	854 (80.6)	1190 (79.0)
≥15 months	965 (84.5)	38 (73.1)	42 (82.4)	72 (78.3)	167 (66.0)	819 (77.3)	1138 (75.5)
≥18 months	706 (61.8)	30 (57.7)	40 (78.4)	57 (62.0)	160 (63.2)	589 (55.6)	876 (58.1)
Duration (months)							
n	1142	52	51	92	253	1059	1507
Mean (SD)	16.31 (4.206)	15.09 (5.325)	16.52 (4.742)	15.28 (5.387)	14.02 (6.555)	15.19 (5.581)	15.04 (5.728)
Median	18.03	18.03	18.49	18.03	18.46	18.00	18.03
Min, max	0.5, 20.0	1.1, 18.3	1.0, 18.9	1.0, 18.5	1.0, 19.0	0.5, 18.8	0.5, 19.0
Total duration (subject-years)[b]	1551.99	65.37	70.21	117.15	295.50	1340.21	1888.44

Pool LEC10-BW

At the 15 April 2022 data cut-off, in Pool LEC10-BW, 1694 subjects were randomised to LEC10-BW, which includes subjects exposed to lecanemab in the Core or OLE Phase of Studies 301 and 201. For subjects who received lecanemab in the Study 201 Core (lower dose or LEC10-BW) and then entered Study 201 OLE Phase, duration of exposure includes the time in Core and in OLE, excluding the Gap Period.

In Pool LEC10-BW, 1268 subjects were exposed to LEC10-BW for at least 6 months, 1014 subjects were exposed to lecanemab for at least 12 months, and 828 subjects were exposed to lecanemab for 18 months.

Overall, in Pool LEC10-BW the mean duration of exposure was 16.49 months, with a minimum of 0.5 months and maximum of 57.9 months.

Adverse events

Study 301 Core

The overall incidence of treatment emergent adverse events (TEAEs) was slightly lower in placebo (81.9%) than LEC10-BW (88.9%). Excluding infusion-related reactions, ARIA-E, and ARIA-H, TEAE rates were similar between placebo (80.2%) and LEC10-BW (83.1%).

Table CS4: Overview of Treatment-emergent AEs (TEAEs) – Study 301 Core (SAS)

Category	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
TEAEs	735 (81.9)	798 (88.9)
Treatment-related TEAEs[a]	197 (22.0)	401 (44.7)
Severe TEAEs	61 (6.8)	67 (7.5)
Serious TEAEs	101 (11.3)	126 (14.0)
Deaths[b]	7 (0.8)	6 (0.7)
Other SAEs[c]	94 (10.5)	120 (13.4)
Life threatening	2 (0.2)	5 (0.6)
Requires inpatient hospitalization or prolongation of existing hospitalization	86 (9.6)	106 (11.8)
Persistent or significant disability or incapacity	1 (0.1)	4 (0.4)
Congenital anomaly/birth defect	0	0
Important medical events	14 (1.6)	18 (2.0)
TEAEs leading to study drug dose adjustment	93 (10.4)	218 (24.3)
TEAEs leading to study drug withdrawal	26 (2.9)	62 (6.9)
TEAEs leading to study drug dose interruption	71 (7.9)	175 (19.5)
TEAEs leading to infusion interruption	11 (1.2)	22 (2.4)
TEAEs of special interest	156 (17.4)	379 (42.2)

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

For each row category, a subject with 2 or more AEs in that category was counted only once. MedDRA Version 25.0 AE = adverse event, MedDRA = medical Dictionary for Regulatory Activities, LEC10-BW = lecanemab 10 mg biweekly, PBO = placebo, SAE = serious adverse event, TEAE = treatment-emergent adverse event. a: Included TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality. b: Included all subjects with SAE resulting in death. c: Included subjects with nonfatal SAEs only. If a subject had both fatal and nonfatal SAEs, the subject was counted in the previous fatal row and was not counted in the nonfatal row.

Table CS5: TEAEs with incidence in ≥2% of subjects in any treatment group by preferred term and decreasing frequency – Study 301 Core (SAS)

MedDRA Preferred Term	Placebo (N = 897) n(%)	Lecanemab 10 mg/kg Biweekly (N = 898) n(%)
Subjects with any TEAE	735 (81.9)	798 (88.9)
Infusion related reaction	64 (7.1)	236 (26.3)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	69 (7.7)	126 (14.0)
Amyloid related imaging abnormality-oedema/effusion	15 (1.7)	113 (12.6)
Headache	73 (8.1)	100 (11.1)
Fall	86 (9.6)	93 (10.4)
Urinary tract infection	82 (9.1)	78 (8.7)
COVID-19	60 (6.7)	64 (7.1)
Back pain	52 (5.8)	60 (6.7)
Arthralgia	62 (6.9)	53 (5.9)
Superficial siderosis of central nervous system	22 (2.5)	50 (5.6)
Dizziness	46 (5.1)	49 (5.5)

Diarrhoea	58	(6.5)	48	(5.3)
Anxiety	38	(4.2)	45	(5.0)
Hypertension	43	(4.8)	41	(4.6)
Contusion	39	(4.3)	38	(4.2)
Fatigue	24	(2.7)	37	(4.1)
Nasopharyngitis	35	(3.9)	36	(4.0)
Pain in extremity	34	(3.8)	32	(3.6)
Nausea	25	(2.8)	31	(3.5)
Vomiting	22	(2.5)	29	(3.2)
Rash	17	(1.9)	29	(3.2)
Upper respiratory tract infection	19	(2.1)	25	(2.8)
Insomnia	21	(2.3)	24	(2.7)
Pyrexia	18	(2.0)	24	(2.7)
Atrial fibrillation	14	(1.6)	24	(2.7)
Depression	38	(4.2)	23	(2.6)
Skin laceration	22	(2.5)	23	(2.6)
Haematuria	7	(0.8)	21	(2.3)
Cough	17	(1.9)	20	(2.2)
Constipation	22	(2.5)	19	(2.1)
Osteoarthritis	14	(1.6)	18	(2.0)
Syncope	12	(1.3)	18	(2.0)

The risk of convulsions is elevated in AD and convulsions have also been reported as a symptom of severe ARIA-E. There were 9 subjects in the study (4 placebo, 5 LEC10-BW) with TEAEs in the standardised MedDRA query (SMQ) of convulsion. Incidence of TEAEs in SMQ of convulsion unassociated with ARIA-E or ARIA-H events, were infrequent and similar between treatment groups (Placebo 3/897: seizure, focal dyscognitive seizures, focal dyscognitive seizures) and LEC10-BW 2/898: seizure, partial seizures). With concurrent ARIA-E or ARIA-H events (Placebo 1/897 and LEC10-BW 3/898: seizure, partial seizures with secondary generalisation, generalized tonic-clonic seizure) reported TEAEs in this SMQ.

Overall, the majority of TEAEs were mild and moderate in severity. Severe TEAEs were reported for placebo (61 [6.8%]) and LEC10-BW (67 [7.5%]). Excluding infusion-related reaction and ARIA, the severity of TEAEs was similar between placebo (6.7%) and LEC10-BW (6.3%).

Overall, the incidence of TEAEs considered by the investigator to be related to study drug was lower in placebo (197 [22.0%]) than LEC10-BW (401 [44.7%]). The most commonly reported (≥2%) treatment-related TEAEs were:

- Infusion-related reaction (placebo 64/897 [7.1%]; LEC10-BW 234/898 [26.1%])
- ARIA-H (placebo 67/897 [7.5%]; LEC10-BW 122/898 [13.6%])
- ARIA-E (placebo 15/897 [1.7%]; LEC10-BW 113/898 [12.6%])
- Superficial siderosis of central nervous system (placebo 20/897 [2.2%]; LEC10-BW 47/898 [5.2%]).

Study 201 Core

The overall incidence of TEAEs was similar across the treatment groups (placebo 87.3%, LEC2.5-BW 88.5%, LEC5-M 92.2%, LEC5-BW 87.0%, LEC10-M 93.7%, and LEC10-BW 85.7%)

Table CS6: Overview of TEAEs – Study 201 Core (SAS)

Category	Placebo (N=245) n (%)	Lecanemab 2.5 mg/kg Biweekly (N=52) n (%)	Lecanemab 5 mg/kg Monthly (N=51) n (%)	Lecanemab 5 mg/kg Biweekly (N=92) n (%)	Lecanemab 10 mg/kg Monthly (N=253) n (%)	Lecanemab 10 mg/kg Biweekly (N=161) n (%)
TEAEs	214 (87.3)	46 (88.5)	47 (92.2)	80 (87.0)	237 (93.7)	138 (85.7)
Treatment-related TEAEs	64 (26.1)	23 (44.2)	25 (49.0)	31 (33.7)	135 (53.4)	76 (47.2)
Severe TEAEs	20 (8.2)	7 (13.5)	2 (3.9)	12 (13.0)	17 (6.7)	16 (9.9)
Serious TEAEs	42 (17.1)	8 (15.4)	4 (7.8)	16 (17.4)	29 (11.5)	21 (13.0)
Deaths[a]	2 (0.8)	2 (3.8)	0	1 (1.1)	1 (0.4)	0
Other SAEs[b]	40 (16.3)	6 (11.5)	4 (7.8)	15 (16.3)	28 (11.1)	21 (13.0)
Life threatening	0	1 (1.9)	0	0	3 (1.2)	0
Requires inpatient hospitalization or prolongation of existing hospitalization	39 (15.9)	6 (11.5)	4 (7.8)	14 (15.2)	24 (9.5)	20 (12.4)
Persistent or significant disability or incapacity	0	0	0	0	0	0
Congenital anomaly / birth defect	0	0	0	0	0	0
Important medical events	5 (2.0)	0	0	2 (2.2)	5 (2.0)	2 (1.2)
TEAEs leading to study drug dose adjustment	48 (19.6)	14 (26.9)	8 (15.7)	24 (26.1)	65 (25.7)	42 (26.1)
TEAEs leading to study drug withdrawal	14 (5.7)	7 (13.5)	4 (7.8)	10 (10.9)	47 (18.6)	24 (14.9)
TEAEs leading to study drug dose reduction	0	0	0	0	0	0
TEAEs leading to study drug dose interruption	36 (14.7)	8 (15.4)	5 (9.8)	15 (16.3)	20 (7.9)	19 (11.8)
TEAEs leading to infusion interruption	6 (2.4)	3 (5.8)	2 (3.9)	5 (5.4)	4 (1.6)	2 (1.2)
TEAEs of special interest	21 (8.6)	7 (13.5)	10 (19.6)	26 (28.3)	88 (34.8)	53 (32.9)

Table CS7: TEAEs by PT and decreasing frequency – incidence ≥5% in highest dose group -Study 201 Core (SAS)

MedDRA Preferred Term	Placebo (N=245) n (%)	Lecanemab 2.5 mg/kg Biweekly (N=52) n (%)	Lecanemab 5 mg/kg Monthly (N=51) n (%)	Lecanemab 5 mg/kg Biweekly (N=92) n (%)	Lecanemab 10 mg/kg Monthly (N=253) n (%)	Lecanemab 10 mg/kg Biweekly (N=161) n (%)
Subjects with any TEAE	214(87.3)	46 (88.5)	47 (92.2)	80 (87.0)	237 (93.7)	138 (85.7)
Infusion-related reaction	8 (3.3)	3 (5.8)	4 (7.8)	11 (12.0)	59 (23.3)	32 (19.9)
Headache	25 (10.2)	8 (15.4)	4 (7.8)	17 (18.5)	41 (16.2)	22 (13.7)
Urinary tract infection	32 (13.1)	5 (9.6)	5 (9.8)	17 (18.5)	24 (9.5)	17 (10.6)
Upper respiratory tract infection	40 (16.3)	7 (13.5)	7 (13.7)	10 (10.9)	23 (9.1)	17 (10.6)
Amyloid related imaging abnormality-oedema/effusion	2 (0.8)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)
Fall	32 (13.1)	3 (5.8)	6 (11.8)	13 (14.1)	21 (8.3)	15 (9.3)
Cough	12 (4.9)	1 (1.9)	2 (3.9)	4 (4.3)	11 (4.3)	14 (8.7)
Nasopharyngitis	28 (11.4)	3 (5.8)	7 (13.7)	9 (9.8)	18 (7.1)	13 (8.1)
Diarrhoea	12 (4.9)	5 (9.6)	7 (13.7)	12 (13.0)	16 (6.3)	13 (8.1)
Dizziness	18 (7.3)	4 (7.7)	0	10 (10.9)	9 (3.6)	12 (7.5)
Back pain	24 (9.8)	4 (7.7)	6 (11.8)	4 (4.3)	18 (7.1)	11 (6.8)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	11 (4.5)	2 (3.8)	7 (13.7)	10 (10.9)	18 (7.1)	9 (5.6)
Fatigue	15 (6.1)	4 (7.7)	1 (2.0)	7 (7.6)	17 (6.7)	8 (5.0)
Arthralgia	19 (7.8)	0	4 (7.8)	7 (7.6)	14 (5.5)	7 (4.3)
Contusion	7 (2.9)	2 (3.8)	5 (9.8)	6 (6.5)	11 (4.3)	7 (4.3)
Hypertension	13 (5.3)	1 (1.9)	1 (2.0)	3 (3.3)	10 (4.0)	7 (4.3)
Nausea	10 (4.1)	1 (1.9)	4 (7.8)	8 (8.7)	14 (5.5)	6 (3.7)
Anxiety	14 (5.7)	1 (1.9)	3 (5.9)	3 (3.3)	10 (4.0)	6 (3.7)
Sinusitis	8 (3.3)	1 (1.9)	5 (9.8)	1 (1.1)	9 (3.6)	6 (3.7)
Depression	13 (5.3)	1 (1.9)	3 (5.9)	6 (6.5)	12 (4.7)	5 (3.1)

There were 3 subjects with TEAEs in the SMQ of convulsions: Placebo 0.4% - 1 subject with seizure, severe, LEC5-BW 1.1% - 1 subject with focal dyscognitive seizures, severe, serious TEAE, and LEC10-M 0.4% - 1 subject with seizure, severe, drug withdrawn, serious TEAE.

Most TEAEs were of mild or moderate intensity. Across treatment groups, the majority of severe TEAEs by preferred term occurred as single events with no dose-related trends in the incidence of severe occurrence for each type of TEAE. However, there was a higher incidence of severe ARIA–E on 10 mg/kg monthly and biweekly compared to placebo or lower doses of lecanemab.

Treatment-related TEAEs were experienced by more subjects in the lecanemab treatment groups than in the placebo group: 65 (26.5%) subjects in the placebo group; 23 (44.2%), 25 (49.0%), 31 (33.7%), 135 (53.4%) and 76 (47.2%) subjects in the BAN2401 2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly and 10 mg/kg biweekly groups, respectively.

Table CS8: Treatment related TEAEs by decreasing frequency of PT (≥3 subjects in any treatment group) – Study 201 Core (SAS)

		BAN2401					
MedDRA Preferred Term	Placebo (N=245) n (%)	2.5 mg/kg Biweekly (N=52) n (%)	5 mg/kg Monthly (N=51) n (%)	5 mg/kg Biweekly (N=92) n (%)	10 mg/kg Monthly (N=253) n (%)	10 mg/kg Biweekly (N=161) n (%)	Total (N=609) n (%)
Subjects with any TEAE	65 (26.5)	23 (44.2)	25 (49.0)	31 (33.7)	135 (53.4)	76 (47.2)	290 (47.6)
Infusion-related reaction	8 (3.3)	3 (5.8)	4 (7.8)	11 (12.0)	58 (22.9)	32 (19.9)	108 (17.7)
Amyloid–related imaging abnormalities	2 (<1.0)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)	46 (7.6)
Cerebral microhaemorrhage	9 (3.7)	2 (3.8)	6 (11.8)	7 (7.6)	21 (8.3)	10 (6.2)	46 (7.6)
Headache	10 (4.1)	3 (5.8)	1 (2.0)	1 (1.1)	25 (9.9)	8 (5.0)	38 (6.2)
Fatigue	6 (2.4)	4 (7.7)	0	1 (1.1)	15 (5.9)	5 (3.1)	25 (4.1)
Superficial siderosis of central nervous system	1 (<1.0)	0	1 (2.0)	5 (5.4)	7 (2.8)	1 (<1.0)	14 (2.3)
Dizziness	3 (1.2)	1 (1.9)	0	1 (1.1)	5 (2.0)	5 (3.1)	12 (2.0)
Nausea	2 (<1.0)	0	2 (3.9)	1 (1.1)	6 (2.4)	1 (<1.0)	10 (1.6)
Diarrhoea	2 (<1.0)	2 (3.8)	3 (5.9)	1 (1.1)	2 (<1.0)	1 (<1.0)	9 (1.5)
Lymphopenia	0	0	0	0	4 (1.6)	4 (2.5)	8 (1.3)
Drug eruption	0	1 (1.9)	0	1 (1.1)	4 (1.6)	1 (<1.0)	7 (1.1)
Anaemia	1 (<1.0)	1 (1.9)	0	0	3 (1.2)	2 (1.2)	6 (<1.0)
Confusional state	1 (<1.0)	1 (1.9)	0	1 (1.1)	3 (1.2)	1 (<1.0)	6 (<1.0)
Pyrexia	0	0	0	2 (2.2)	4 (1.6)	0	6 (<1.0)
Decreased appetite	0	0	0	0	4 (1.6)	0	4 (<1.0)
Hot flush	2 (<1.0)	0	0	0	4 (1.6)	0	4 (<1.0)

Pool Core and Pool LEC10-BW

In Pool Core, consistent with Study 301 Core, the overall incidence of TEAEs was 83.1% in the placebo group and 88.4% in the LEC10-BW group.

In Pool Core, the most common TEAEs occurring in subjects were consistent with Study 301 Core and include infusion-related reaction, ARIA-H, ARIA-E, and headache.

In Pool LEC10-BW, consistent with Study 301 Core, the overall incidence of TEAEs in LEC10-BW was 82.6%. The incidence of the most common (≥5%) TEAEs were the same as Study 301 Core.

Summary

The main safety signals associated with the use of monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, are amyloid related imaging abnormalities (ARIA), intracerebral haemorrhage, infusion-related reactions (IRR) and hypersensitivity.

In the pivotal study 301 Core, the overall incidence of TEAEs was higher in the LEC10-BW (88.9%) group compared with placebo (81.9%). The overall incidence was similar in both groups when events of IRR, ARIA-E and ARIA-H were excluded (83.1% vs 80.2%). The majority of TEAEs were mild or moderate in severity. Severe TEAEs were reported 7.5% of LEC10-BW subjects and 6.8% for placebo, and when excluding IRRs and ARIA the incidence was similar in both groups (6.3% vs 6.7%). The incidence of AE considered treatment-related in the LEC10-BW group (44.7%) was double that in the placebo group (22.0%).

The most common TEAEs with an incidence ≥5% that occurred more commonly in LEC10-BW than placebo were IRR (26.3% vs 7.1%), ARIA-H (cerebral microhaemorrhage [14% vs 7.7%]), ARIA-E (12.6% vs 1.7%), headache (11.1% vs 8.1%) and superficial siderosis of central nervous system (5.6% vs 2.5%).

'Infusion-related reactions', 'ARIA-E', 'ARIA-H' (microhaemorrhage and haemosiderin deposit; Superficial siderosis of central nervous system, and Cerebellar microhaemorrhage) and 'headache' are considered to be adverse drug reactions (ADR) for LEC10-BW and have been included in the SmPC.

In study 201 core, the overall incidence of TEAEs was similar across the treatment groups. The majority of TEAEs were mild or moderate in severity. Similar to study 301 core, the most common TEAEs with an incidence ≥5% that occurred more commonly in LEC10-BW than placebo were IRR (25.3% vs 6.3%), ARIA-H (cerebral microhaemorrhage [12.7% vs 7.0%]), ARIA-E (12.2% vs 1.5%) and headache (11.5% vs 8.6%).

In the Pool Core and Pool LEC10-BW, the overall incidence of TEAEs was similar to that seen in Study 301 Core.

Incidence of TEAEs in SMQ of convulsion associated with ARIA-E or ARIA-H events, were infrequent and similar between treatment groups and similar in Study 301 Core and 201 Core. Seizures were an infrequent symptom of ARIA-E.

In study 301 core the incidence of treatment-emergent atrial fibrillation (AF) was 24 subjects (2.7%) in the LEC10-BW group and 14 (1.6%) in placebo. Treatment emergent serious AEs of AF were reported in 6 subjects (0.7%) in the LEC10-BW group and 3 subjects (0.3%) in placebo. In study 201 core the incidence of treatment-emergent AF was 6 subjects (3.7%) in the LEC10-BW group and 4 (1.6%) in placebo. Given the imbalance in the incidence of atrial fibrillation observed across both studies, atrial fibrillation was considered to be an ADR for LEC10-BW and was included in the SmPC.

Hypersensitivity reactions are a known safety signal with the use of monoclonal antibodies directed against aggregated forms of beta amyloid. In study 301 core, there was a higher incidence of hypersensitivity reported in the LEC10-BW group (1.7%), all of which were considered related to treatment, compared with placebo (0.9%). In addition, a grade 4 IRR that occurred in a subject was in fact considered to be an anaphylactic reaction. There was also a higher incidence of 'rash' in the LEC10-BW group (3.2%) compared with placebo (1.9%). 'Hypersensitivity reactions', 'anaphylaxis' and 'rash' are considered to be adverse drug reactions (ADR) for LEC10-BW and have been included in the SmPC.

Updated safety data was provided for study 201 OLE, study 301 OLE and Pool LEC10 BW with a data cut-off 01 December 2022. Overall, the most common TEAEs reported in Study 301 OLE Phase (LEC10-BW Treated Period) and Study 201 OLE Phase were consistent with what was reported in the Core studies.

Serious adverse events and deaths

Deaths

As of the reporting period (up to 13 September 2022 for Study 301 Core and 15 April 2022 for ongoing studies), a total of 30 subjects died.

Study 301

Table CS9: Treatment emergent AEs leading to death by SOC and PT – Study 301 Core (SAS)

MedDRA System Organ Class Preferred Term	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
Subjects with any TEAE leading to death	7 (0.8)	6 (0.7)
Cardiac disorders	1 (0.1)	1 (0.1)
Myocardial infarction	1 (0.1)	1 (0.1)
General disorders and administration site conditions	1 (0.1)	1 (0.1)
Death	1 (0.1)	1 (0.1)
Infections and infestations	1 (0.1)	1 (0.1)
COVID-19	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2)	1 (0.1)
Metastases to bone	1 (0.1)	0
Metastases to meninges	0	1 (0.1)
Pancreatic carcinoma	1 (0.1)	0
Nervous system disorders	1 (0.1)	1 (0.1)
Cerebrovascular accident	0	1 (0.1)
Haemorrhage intracranial	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1 (0.1)
Acute respiratory failure	1 (0.1)	0
Respiratory failure	0	1 (0.1)

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subject with 2 or more AEs in the same system organ class (or with the same preferred term) was counted only once for that system organ class (or preferred term). Cerebral microhemorrhages included those deemed not ARIA-H by investigator.

There were 2 additional, not treatment-emergent deaths that occurred more than 30 days after the last treatment administration: One in the placebo group due to cardio-respiratory arrest, one in LEC10 BW due to diabetic ketoacidosis. None of the 15 deaths were considered related to study drug.

There were 3 additional deaths in the OLE phase: 2 in subjects that received placebo in the core study due to myocardial infarction, and COVID-19 pneumonia; and one in a subject that received LEC10-BW in the core study due to cardiac failure acute. None of the 3 deaths were considered related to study drug.

Study 201

In Study 201 Core, there were 6 treatment-emergent deaths, 2 in the placebo group (acute respiratory failure, sarcoma) and 4 in the lecanemab treatment groups (neoplasm with surrounding vasogenic oedema, cardiac arrest, multiple organ dysfunction syndrome, spinal cord injury). There was 1 additional, not treatment-emergent death in the LEC10-M group (respiratory failure).

All of the deaths were considered not related to study drug except for one subject in the LEC2.5-BW group (neoplasm with surrounding vasogenic oedema) which was assessed by the investigator as possibly related to study drug. The post-mortem examination showed a glioblastoma (WHO Grade IV). Given the relatively short duration of treatment compared to the latency for the development of malignancies and the low treatment dose, it is considered unlikely that this fatal event was due to study drug.

In the OLE Phase, 3 deaths were reported as treatment-emergent (metastases to central nervous system, cervical vertebral fracture, neuroendocrine carcinoma and malignant neoplasm of unknown primary site) and an additional 2 not treatment-emergent deaths (COVID-19 pneumonia, dementia Alzheimer's type). All 5 deaths were considered not related to study drug.

Updated data submitted on patient deaths
An additional 6 deaths were reported up to 01 December 2022, all in the OLE phase of study 301. Of the 6 new deaths reported, 2 were not considered related to treatment (COVID-19, road traffic accident). The remaining 4 deaths were treatment-emergent and considered possibly related to treatment.

Of the 4 deaths that were considered possibly related to treatment, 2 occurred in ApoE4 homozygous patients. These patients received placebo in the core study and the events leading to death occurred early in the open label extension after their 3rd dose of lecanemab. One died after severe ARIA-E and ARIA-H, and the second with multiple intracerebral haemorrhages after receiving tissue plasminogen activator (tPA). Autopsy findings revealed a high burden of Cerebral Amyloid Angiopathy (CAA) and findings consistent with an inflammatory vasculitis. The inflammatory vasculitis resembled CAA related inflammation, a spontaneous inflammatory response to vascular amyloid deposits. Appropriate warnings regarding use of thrombolytic agents in patients being treated with lecanemab are included in the SmPC.

There is a high background rate of CAA in AD which increases with the number of ApoE4 alleles. Patients were not enrolled in the clinical trials if they had MRI findings consistent with CAA at baseline and this is reflected in section 4.3 and 5.1 of the SmPC. However, many individuals with CAA do not have the characteristic findings on MRI. The risk of severe CAA and CAA related inflammation is highest in ApoE4 homozygous patients. Lecanemab is not indicated for use in ApoE4 homozygous patients.

The 3rd death occurred in a patient that was an ApoE4 non-carrier who received placebo in the core study. This patient had cardiovascular disease and was receiving anticoagulants. The concurrent medical events in this case complicate the causality assessment, however, the investigator classified the events of ARIA-H (microhaemorrhages), ARIA-E, ARIA-H (macrohaemorrhage) cerebral haemorrhage, and transient ischaemic attack to be related to the study drug. Appropriate contraindications and warnings regarding concomitant anticoagulation therapy with lecanemab are included in the SmPC.

The 4th death reported in the OLE of study 301 occurred in a patient that was an ApoE4 non-carrier that received lecanemab 10mg/kg biweekly in the core phase of the study. The patient was suspected to have experienced a symptomatic cerebral vascular accident (CVA) 9 days after their 9th dose of lecanemab in the extension phase. There was no reported relevant past medical history or concomitant medications in the OLE. The patient died due to suspected CVA and cardiorespiratory arrest. An autopsy was not performed.

From 01 December 2022 through to 30 November 2023 (301 OLE) and 01 November 2023 (201 OLE) there were 12 additional deaths (48 total for the lecanemab program) across the lecanemab program.

Of the 12 additional deaths, none were due to ARIA or intracerebral haemorrhage. One death due to interstitial pneumonia was considered possibly related to study treatment, although assessment of causality in this isolated case is difficult. Of the remaining 11 deaths considered not related to treatment, 6 were due to carcinomas, the remaining 5 were due to pneumonia, acute myocardial infarction, cardiac failure, sudden cardiac death, confusion and delirium.

Serious adverse events

Study 301 Core
The incidence of serious TEAEs was 11.3% in the placebo group and 14.0% in LEC10-BW. Excluding events of infusion-related reactions, ARIA-E, and ARIA-H, the incidence of serious TEAEs was similar between placebo (11.3%) and LEC10-BW (12.4%).

Table CS10: TESAEs occurring in ≥2 subjects by decreasing frequency – Study 301 Core (SAS)

MedDRA Preferred Term	Placebo (N = 897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)
Subjects with any treatment-emergent SAE	101 (11.3)	126 (14.0)
Infusion-related reaction	0	11 (1.2)
Amyloid related imaging abnormality-oedema/effusion	0	7 (0.8)
Atrial fibrillation	3 (0.3)	6 (0.7)
Syncope	1 (0.1)	6 (0.7)
Angina pectoris	0	6 (0.7)
Diverticulitis	1 (0.1)	4 (0.4)
Non-cardiac chest pain	0	4 (0.4)
Pneumonia	3 (0.3)	3 (0.3)
Subdural haematoma	3 (0.3)	3 (0.3)
Hip fracture	2 (0.2)	3 (0.3)
Inguinal hernia	2 (0.2)	3 (0.3)
Transient ischaemic attack	2 (0.2)	3 (0.3)
Fall	1 (0.1)	3 (0.3)
Cerebral haemorrhage	0	3 (0.3)
Acute respiratory failure	3 (0.3)	2 (0.2)
Osteoarthritis	3 (0.3)	2 (0.2)
COVID-19	2 (0.2)	2 (0.2)
Dehydration	2 (0.2)	2 (0.2)
Cerebrovascular accident	1 (0.1)	2 (0.2)
Femoral neck fracture	1 (0.1)	2 (0.2)
Acute kidney injury	0	2 (0.2)
Acute myocardial infarction	0	2 (0.2)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	0	2 (0.2)
COVID-19 pneumonia	0	2 (0.2)
Cellulitis	0	2 (0.2)
Coronary artery disease	0	2 (0.2)
Diarrhoea	0	2 (0.2)
Hyponatraemia	0	2 (0.2)
Invasive ductal breast carcinoma	0	2 (0.2)
Pulmonary oedema	0	2 (0.2)
Respiratory failure	0	2 (0.2)
Thoracic vertebral fracture	0	2 (0.2)
Ankle fracture	3 (0.3)	1 (0.1)
Prostate cancer	3 (0.3)	1 (0.1)
Pulmonary embolism	3 (0.3)	1 (0.1)
Myocardial infarction	2 (0.2)	1 (0.1)
Confusional state	3 (0.3)	0
Spinal compression fracture	3 (0.3)	0
Adenocarcinoma of colon	2 (0.2)	0
Intraductal proliferative breast lesion	2 (0.2)	0
Small intestinal obstruction	2 (0.2)	0
Spondylolisthesis	2 (0.2)	0

The incidence of treatment-related, TESAEs were lower in placebo (0.6%) than LEC10-BW (2.7%). Most events were reported by single subjects in either group apart from infusion-related reactions (1.2%), ARIA-E (0.8%), ARIA-H (0.2%), and cerebral haemorrhage (0.2%), which were only reported in LEC10-BW. 'Infusion-related reactions', ARIA-E, ARIA-H and 'intracerebral haemorrhage' are considered ADRs with lecanemab and are included in the SmPC.

After IRRs and ARIA-E, the most commonly reported TESAEs were atrial fibrillation, syncope and angina. These were each reported in 6 subjects (0.7%) in the LEC10-BW group vs 3 (0.3%), 1 (0.1%) and 0 subjects in the placebo group respectively.

Atrial fibrillation is considered an ADR with lecanemab and is included in the SmPC. Serious events of syncope and angina pectoris are expected in the elderly patient population and following analyses of these events in study 201 and 301, these events are not considered to be ADRs with lecanemab.

Study 201 Core

The incidence of TESAEs was similar across the treatment groups with no evidence of a dose response. The incidence of treatment-related SAEs was 2.5% in LEC10-BW and 1.6% in the placebo group. The most frequent (2 subjects or more) treatment-related TESAEs in the lecanemab 10 mg/kg biweekly group were: ARIA–E (1.9%), and cerebral microhaemorrhage (1.2%).

Table CS11: TESAEs by SOC and PT (≥2 subjects in any treatment group with event by PT) – SAS

MedDRA SOC Preferred Term	Placebo (N=245) n (%)	BAN2401					
		2.5 mg/kg Biweekly (N=52) n (%)	5 mg/kg Monthly (N=51) n (%)	5 mg/kg Biweekly (N=92) n (%)	10 mg/kg Monthly (N=253) n (%)	10 mg/kg Biweekly (N=161) n (%)	Total (N=609) n (%)
Subjects with any TESAE	43 (17.6)	10 (19.2)	4 (7.8)	16 (17.4)	31 (12.3)	25 (15.5)	86 (14.1)
General disorders and administration site conditions	2 (<1.0)	0	0	3 (3.3)	2 (<1.0)	4 (2.5)	9 (1.5)
Non-cardiac chest pain	0	0	0	0	2 (<1.0)	2 (1.2)	4 (<1.0)
Injury, poisoning and procedural complications	13 (5.3)	1 (1.9)	1 (2.0)	1 (1.1)	4 (1.6)	4 (2.5)	11 (1.8)
Fall	4 (1.6)	0	0	0	1 (<1.0)	0	1 (<1.0)
Subdural haematoma	2 (<1.0)	1 (1.9)	0	0	0	1 (<1.0)	2 (<1.0)
Musculoskeletal and connective tissue disorders	5 (2.0)	0	0	2 (2.2)	1 (<1.0)	3 (1.9)	6 (1.0)
Arthralgia	0	0	0	1 (1.1)	0	2 (1.2)	3 (<1.0)
Osteoarthritis	4 (1.6)	0	0	0	0	0	0
Nervous system disorders	9 (3.7)	1 (1.9)	2 (3.9)	6 (6.5)	6 (2.4)	6 (3.7)	21 (3.4)
Amyloid–related imaging abnormalities	0	0	0	0	1 (<1.0)	3 (1.9)	4 (<1.0)
Cerebral microhaemorrhage	0	0	0	0	0	2 (1.2)	2 (<1.0)
Syncope	3 (1.2)	0	0	1 (1.1)	1 (<1.0)	1 (<1.0)	3 (<1.0)
Transient ischaemic attack	1 (<1.0)	0	2 (3.9)	0	1 (<1.0)	1 (<1.0)	4 (<1.0)
Respiratory, thoracic and mediastinal disorders	1 (<1.0)	2 (3.8)	0	0	4 (1.6)	4 (2.5)	10 (1.6)
Dyspnoea	0	0	0	0	0	2 (1.2)	2 (<1.0)
Pulmonary embolism	0	0	0	0	1 (<1.0)	2 (1.2)	3 (<1.0)
Pulmonary mass	0	2 (3.8)	0	0	0	0	2 (<1.0)

The SAEs were assessed by the investigator as related to study drug in: 4 (1.6%) subjects in the placebo group; 3 (5.8%), 2 (2.2%), 2 (<1.0%), and 4 (2.5%) subjects in lecanemab 2.5 mg/kg biweekly, 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly groups, respectively, and 11 (1.8%) subjects in the lecanemab treatment groups overall.

Pool Core

The incidence of serious TEAEs was consistent with the results of Study 301 Core with an incidence of 12.5% in the placebo group and 13.9% in LEC10-BW.

Pool LEC10-BW

In Pool LEC10-BW, consistent with Study 301 Core, the incidence of serious TEAEs was 251 (14.8%). The majority of serious TEAEs occurred in 5 or fewer subjects. Events occurring in 7 or more subjects were: infusion-related reaction (20 [1.2%]), ARIA-E (15 [0.9%]), atrial fibrillation (10 [0.6%]), fall (8 [0.5%]), pneumonia (8 [0.5%]), syncope (8 [0.5%]), angina pectoris (7 [0.4%]), non-cardiac chest pain (7 [0.4%]), and transient ischemic attack (7 [0.4%]).

Adverse events of special interest

Adverse events of special interest included infusion-related reactions, skin rash related to study drug, other hypersensitivity reactions related to study drug, ARIA-E, ARIA-H, suicidal behaviour, and suicidal ideation.

Infusion-related reactions

Study 301 Core

Table CS12: Summary of IRRs by maximum grade – Study 301 Core (SAS)

NCI-CTCAE Grade	Placebo (N = 897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)
Any grade	66 (7.4)	237 (26.4)
Grade 1	41 (4.6)	78 (8.7)
Grade 2	25 (2.8)	149 (16.6)
Grade 3	0	6 (0.7)
Grade 4	0	1 (0.1)
Grade 5	0	0
Missing	0	3 (0.3)

Of the LEC10-BW subjects who experienced infusion-related reaction, severity was as follows: Grade 1: 78/237 (32.9%), Grade 2: 149/237 (62.9%), Grade 3: 6/237 (2.5%), Grade 4: 1/237 (0.4%).

Of the 7 subjects that experienced severe (≥ grade 3) IRRs, all required more intensive evaluation at secondary centres, received supportive therapy, almost all resolved between Days 1 and 4 post reaction, and all were discharged without further incident. All were discontinued from study drug per protocol.

The majority of infusion-related reactions occurred with the first infusion, (placebo 39.4%, LEC10-BW 75.1%). Of the 7 subjects that reported grade 3 or 4 IRRs, 6 occurred with the first dose. Most subjects who reported infusion-related reactions returned for the next study visit (placebo 97.0%, LEC10-BW 93.7%).

Of the 222 subjects (93.7%) in the LEC10-BW group who continued to the next visit, 97 (43.7%) received at least 1 preventative medication with subsequent infusions (e.g., ibuprofen, paracetamol, and diphenhydramine). Of these 97 subjects, 36/97 (37.1%) had subsequent infusion-related reactions and 61/97 (62.9%) did not. There was a similar rate of recurrence regardless of use of preventative medications (35.2% in subjects that did not receive a preventative medication with subsequent infusions).

There were few TEAEs of infusion-related reaction and infusion site reaction leading to study drug interruption (placebo 0.7%; LEC10-BW 1.6%) or infusion interruption (placebo 0.1%; LEC10-BW 1.0%). There were no infusion-related TEAEs considered as TESAEs on placebo and 11 (1.2%) on LEC10-BW.

Study 201 Core

Table CS13: Summary of IRRs by maximum grade – Study 201 Core (SAS)

NCI-CTCAE Grade	Placebo (N=245) n (%)	Lecanemab 2.5 mg/kg Biweekly (N=52) n (%)	Lecanemab 5 mg/kg Monthly (N=51) n (%)	Lecanemab 5 mg/kg Biweekly (N=92) n (%)	Lecanemab 10 mg/kg Monthly (N=253) n (%)	Lecanemab 10 mg/kg Biweekly (N=161) n (%)
Any grade	8 (3.3)	3 (5.8)	4 (7.8)	12 (13.0)	59 (23.3)	32 (19.9)
Grade 1	4 (1.6)	2 (3.8)	3 (5.9)	2 (2.2)	15 (5.9)	10 (6.2)
Grade 2	4 (1.6)	1 (1.9)	1 (2.0)	9 (9.8)	40 (15.8)	19 (11.8)
Grade 3	0	0	0	0	4 (1.6)	2 (1.2)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Missing	0	0	0	1 (1.1)	0	1 (0.6)

One subject (LEC10-BW) reported a serious TEAE of IRR (Grade 3) that was considered probably related to study drug and was hospitalized. The subject was discharged after symptomatic treatment and lecanemab was discontinued per protocol.

Two (0.8%) subjects in the placebo group, 5 subjects (2.0%) in the LEC10-M and 4 (2.5%) subjects in the LEC10-BW group had IRRs that led to discontinuation of study drug.
The majority of IRRs occurred with the first infusion. Most subjects who reported IRRs received preventative medications with subsequent infusions, and greater than 70% of LEC10-BW subjects did not report further IRRs, regardless of preventative medication.

Pool Core

Consistent with Study 301 Core, the overall incidence of IRRs was lower in placebo (74/1142 [6.5%]) than LEC10-BW (269/1059 [25.4%]).

Pool LEC10-BW

Table CS14: Summary of IRRs by maximum grade – Pool LEC10-BW (SAS)

NCI-CTCAE Grade	Lecanemab 10 mg/kg Biweekly (N=1694) n (%)
Any grade	410 (24.2)
Grade 1	132 (7.8)
Grade 2	262 (15.5)
Grade 3	10 (0.6)
Grade 4	1 (0.1)
Grade 5	0
Missing	5 (0.3)

Summary
In studies 201 and 301, IRRs were very common in subjects treated with lecanemab with symptoms including fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation. The majority of IRRs were of mild or moderate severity and occurred with the first dose. Most reactions including severe reactions occurred during the infusion or within approximately 2.5 hours after infusion completion. Rates of discontinuation due to IRRs were low. The majority of subjects did not report further IRRs (>63% in study 301 core and >70% of LEC10-BW subjects in study 201 core). There was a similar rate of recurrence regardless of use of preventative medications e.g., ibuprofen, paracetamol, and diphenhydramine.

In study 301 core, 6 (0.7%) subjects reported a grade 3 IRR and 1 subject (0.1%) reported a grade 4 IRR. Of the 7 subjects that reported grade 3 or 4 IRRs, 6 occurred with the first dose. All 7 required more intensive evaluation at secondary centres, received supportive therapy, almost all resolved between Days 1 and 4 post reaction, and all were discharged without further incident. All were discontinued from study drug in accordance with the study protocol. The grade 4 IRR that occurred after their first dose of study drug was in fact considered to be an anaphylactic reaction and epinephrine was administered.

In study 201 a dose response was seen with higher rates of IRR with increasing dose. Grade 3 reactions were only reported at the highest 2 doses (10mg/month and 10mg biweekly).

Appropriate warnings regarding IRRs and hypersensitivity reactions including anaphylaxis are included in the SmPC.

ARIA

Monoclonal antibodies directed against aggregated forms of beta amyloid can cause amyloid related imaging abnormalities (ARIA), characterised as ARIA with oedema (ARIA-E), which can be observed on MRI as brain oedema or sulcal effusions, and ARIA with haemosiderin deposition (ARIA-H), which includes microhaemorrhage and superficial siderosis. It is hypothesized that anti-Aβ antibodies accelerate breakdown and clearance of Aβ, which may disrupt vascular integrity and result in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI.

Microhaemorrhage and superficial siderosis, as well as mild focal oedema, can occur spontaneously in patients with Alzheimer's disease in the absence of treatment with amyloid targeting therapies. This may be related to underlying amyloid burden or cerebral amyloid angiopathy and are usually observed as incidental findings on MRI. Routine safety monitoring for ARIA was undertaken in the clinical trials for lecanemab. In the pivotal study 301 core, a baseline MRI was obtained prior to initiating treatment and core central reading of MRIs performed at weeks 9, 13, 27, 53, 79 and at the 3-month follow-up visit was undertaken.

ARIA-E
Study 301 Core
Incidence

Table CS15: Summary of treatment-emergent ARIA-E – Study 301 Core (SAS)

ARIA Term	PBO (N = 897) n/m (%)	LEC10-BW (N = 898) n/m (%)
ARIA-E	15 (1.7)	113 (12.6)
APOE4 noncarriers	1/286 (0.3)	15/278 (5.4)
APOE4 carriers	14/611 (2.3)	98/620 (15.8)
APOE4 heterozygous carriers	9/478 (1.9)	52/479 (10.9)
APOE4 homozygous carriers	5/133 (3.8)	46/141 (32.6)

A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. A subject with 2 or more events is counted only once for that event.

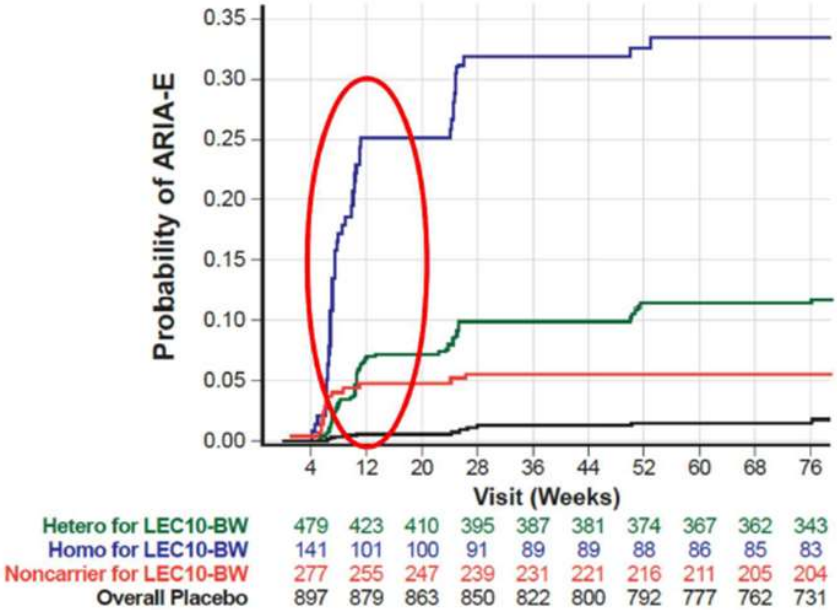
Table CS16: Treatment-emergent serious ARIA-E – Study 301 Core (SAS)

ARIA Term	Placebo (N = 897) n/m (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n/m (%)
Serious ARIA-E	0	7 (0.8)
APOE4 noncarriers	0/ 286	2/ 278 (0.7)
APOE4 carriers	0/ 611	5/ 620 (0.8)
APOE4 heterozygous carriers	0/ 478	2/ 479 (0.4)
APOE4 homozygous carriers	0/ 133	3/ 141 (2.1)

There were no cases of ARIA-E leading to study discontinuation in placebo and 14 (1.6%) in LEC10-BW.

Timing

Figure CS1: Kaplan-Meier curve of time to first ARIA-E – Study 301 Core (SAS)



Radiographic severity

Table CS17: Maximum radiographic severity of ARIA-E - study 301 core (SAS)

	Placebo				**LEC10-BW**			
	Overall (n=897)	*APOE4 non carriers (n=286)*	*APOE4 heterozygotes (n=478)*	*APOE4 homozygotes (n=133)*	*Overall (n=898)*	*APOE4 non carriers (n=278)*	*APOE4 heterozygotes (n=479)*	*APOE4 homozygotes (n=141)*
Mild	9/897 (1.0%)	0	7/478 (1.5%)	2/133 (1.5%)	37/898 (4.1%)	6/278 (2.2%)	25/479 (5.2%)	6/141 (4.3%)
Moderate	6/897 (0.7%)	1/286 (0.3%)	2/478 (0.4%)	3/133 (2.3%)	66/898 (7.3%)	9/278 (3.2%)	24/479 (5.0%)	33/141 (23.4%)
Severe	0	0	0	0	9/898 (1.0%)	0	2/479 (0.4%)	7/141 (5.0%)
Missing	0	0	0	0	0	0	1/479 (0.2%)	0

Symptoms

Table CS18: Symptomatic ARIA-E - study 301 core (SAS)

	Placebo				**LEC10-BW**			
	Overall (n=897)	*APOE4 non carrier (n=286)*	*APOE4 heterozygote (n=478)*	*APOE4 homozygote (n=133)*	*Overall (n=898)*	*APOE4 non carriers (n=278)*	*APOE4 heterozygote (n=479)*	*APOE4 homozygote (n=141)*
Symptomatic ARIA-E	0	0	0	0	25/898 (2.8%)	4/278 (1.4%)	8/479 (1.7%)	13/141 (9.2%)
Symptoms category[a]								
Symptomatic mild	0	0	0	0	10/898 (1.1%)	1/278 (0.4%)	4/479 (0.8%)	5/141 (3.5%)
Symptomatic moderate	0	0	0	0	12/898 (1.3%)	3/278 (1.1%)	2/479 (0.4%)	7/141 (5.0%)
Symptomatic severe	0	0	0	0	3/898 (0.3%)	0	2/479 (0.4%)	1/141 (0.7%)

Symptoms occurring in more than 1 subject in LEC10-BW were headache (12), confusional state (4), dizziness (3), and nausea (3).

Resolution

The majority (81%) of ARIA-E resolved by 4 months since onset. All 113 cases of first ARIA-E in LEC10-BW subjects resolved. In placebo, of the 15 subjects experiencing first ARIA-E, 12 resolved and 3 remained ongoing.

Investigators were permitted to continue dosing without interruption for radiographically mild asymptomatic ARIA-E at onset. Fifty-four subjects had radiographically mild ARIA-E at onset:

- 32 of the 54 subjects had ARIA-E that resolved spontaneously without dose interruption.
- 10 of the 54 subjects had dose interruption, per investigator decision, after the first MRI with ARIA-E, and the ARIA-E resolved.
- 12 of the 54 subjects continued dosing after the first MRI with ARIA-E, the ARIA-E

became radiographically moderate and had dose interruptions, then the subjects' ARIA-E resolved.

All symptomatic ARIA-E resolved during the core period of study 301 with the exception of 1 subject that had residual headache.

Recurrence

ARIA-E was observed in 13% (113/898) of patients treated with lecanemab, of which 85% (96/113) continued on lecanemab treatment with or without dose interruption. Among those that continued lecanemab, 29% (28/96) experienced a recurrence of ARIA-E. By ApoE4 status the recurrence rates were 9% (1/11) in non-carriers, 15% (7/48) in heterozygotes and 54% (20/37) in homozygotes.

There is no apparent worsening in severity or resolution rates with recurrent events.

Potential impact of ARIA-E (and ARIA-H) on cognition or function

In Study 301 Core, the majority of subjects who experienced ARIA had post-ARIA CDR-SB assessment after onset of the last treatment-emergent ARIA (PBO: 85/85 [100%], LEC10-BW 184/193 [95%]), which are included in the primary analysis. ARIA as a time-varying covariate was not statistically significant. Multiple analyses were performed to assess the impact of ARIA on cognition and function, which included incorporating data after ARIA events (primary MMRM), censoring data after ARIA events, and incorporating ARIA as a covariate. Analyses was also performed imputing the data after ARIA events with mean PBO.

Figure CS2: sensitivity analyses of CDR-SB for ARIA

Type of Sensitivity Analysis	Adjusted Mean Change from Baseline at 18 Months		Treatment Difference at 18 Months	% Slowing	p-value
	Placebo	Lecanemab			
MMRM censoring assessments after occurrence of ARIA (ARIA-E or ARIA-H) Analysis set = ITT FAS+	1.675	1.151	-0.524	31.3	<.00001
MMRM censoring assessments after occurrence of ARIA-E[1] Analysis set = ITT FAS+	1.672	1.169	-0.503	30.1	0.00001
MMRM censoring assessments after occurrence of ARIA-H Analysis set = ITT FAS+	1.661	1.162	-0.499	30.0	0.00001

Type of Sensitivity Analysis	Adjusted Mean Change from Baseline at 18 Months		Treatment Difference at 18 Months	% Slowing	p-value
	Placebo	Lecanemab			
MMRM imputing assessments after occurrence of ARIA (ARIA-E or ARIA-H) Analysis set = ITT FAS+	1.678	1.235	-0.443	26.4%	0.000005
MMRM imputing assessments after occurrence of ARIA-E[1] Analysis set = ITT FAS+	1.679	1.222	-0.457	27.2%	0.0000147
MMRM imputing assessments after occurrence of ARIA-H Analysis set = ITT FAS+	1.670	1.222	-0.448	26.8%	0.000006

In addition, analysis of individual clinical outcomes (CDR-SB) for subjects with single or multiple ARIA-E events show no pattern of adverse impact on cognition and function.

Study 201 Core

Table CS19: Treatment emergent ARIA-E by ApoE4 status – Study 201 Core (SAS)

ARIA Term	Placebo (N=245) n/m (%)	Lecanemab				
		2.5 mg/kg Biweekly (N=52) n/m (%)	5 mg/kg Monthly (N=51) n/m (%)	5 mg/kg Biweekly (N=92) n/m (%)	10 mg/kg Monthly (N=253) n/m (%)	10 mg/kg Biweekly (N=161) n/m (%)
ARIA-E	2 (0.8)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)
APOE4 noncarriers	0/ 71	0/ 14	0/ 11	0/ 8	2/ 28 (7.1)	9/ 112(8.0)
APOE4 carriers	2/174 (1.1)	1/38 (2.6)	1/40 (2.5)	3/84 (3.6)	23/225 (10.2)	7/49 (14.3)
APOE4 heterozygous carriers	1/134 (0.7)	1/33 (3.0)	0/28	2/70 (2.9)	12/165 (7.3)	2/39 (5.1)
APOE4 homozygous carriers	1/40 (2.5)	0/5	1/12 (8.3)	1/14 (7.1)	11/60 (18.3)	5/10 (50.0)

ARIA-E events in placebo were randomly distributed over the course of treatment. Most cases of treatment-emergent ARIA-E in LEC10-BW occurred within the first 3 months of treatment.

Most treatment emergent ARIA–E were radiographically mild (placebo 1/245 [0.4%]; LEC10-BW 7/161 [4.3%]) or moderate (placebo 0/245 [0.0 %]; LEC10-BW 7/161 [4.3 %]) in severity; with no subjects in placebo and 2/161 (1.2 %) subjects in LEC10-BW categorized as having radiographically severe ARIA–E. The percentage of radiographically moderate severity ARIA-E was higher in the homozygous ApoE4 carriers.

The incidence of symptomatic ARIA-E was low, with no subjects in placebo and LEC10-BW 5/161 (3.1%). Of those subjects that reported symptomatic ARIA-E, the clinical severity rates were as follows:
• ApoE4 noncarriers: moderate 1/1 (100%) and no severe ARIA-E
• Heterozygous ApoE4 carriers: no moderate ARIA-E and no severe ARIA-E
• Homozygous ApoE4 carriers: no moderate ARIA-E and severe ARIA-E 3/4 (75.0%)

The majority (75%) of ARIA-E resolved by 4 months of onset. All 16 cases of ARIA-E in subjects treated with LEC10-BW resolved.

Pool LEC10-BW
ARIA-E was similar to that reported in Study 301 Core, including characteristics of incidence (overall and by ApoE4 genotype), radiographic severity, and time to onset.

Summary
In study 301 core, ARIA-E was very common in the LEC10-BW group with an overall incidence of 12.6% compared with 1.7% in the placebo group 1.7%. The incidence of ARIA-E with LEC10-BW was much higher in ApoE4 homozygous patients (32.6%) compared with heterozygotes (10.9%) and non-carriers (5.4%).

No patients in the placebo group experienced an event of serious ARIA-E. The incidence of serious events of ARIA-E in LEC10-BW treated patients was low (0.9%). The incidence was highest in ApoE4 homozygous patients (2.1%) compared with heterozygotes (0.4%) and non-carriers (0.7%).

The incidence of events of ARIA-E leading to discontinuation was low and only occurred in the LEC10-BW group (14 subjects [1.6%]).

Whilst events of ARIA-E in placebo were randomly distributed over the course of treatment, for the first episode of ARIA-E, most cases of LEC10-BW treatment-emergent ARIA-E occurred within the first 3 months of treatment (70.9%) i.e., within the first 7 doses and very few occurred after 6 months. The timing of events of ARIA-E was the same regardless of genotype.

Most treatment-emergent ARIA–E were radiographically mild or moderate in severity. No subjects in the placebo group and 9 (1% [8% of subjects with ARIA-E]) subjects in LEC10-BW were categorized as having radiographically severe ARIA–E. The incidence of severe radiographic ARIA-E was higher in ApoE4 homozygotes (5%) compare with heterozygotes (0.4%) and non-carriers (0%).

Most ARIA-E events were asymptomatic. Symptomatic ARIA-E occurred in 25 subjects (2.8%, [22% of subjects with ARIA-E]) in the LEC10-BW and no subjects on placebo. The incidence of symptomatic ARIA-E was much higher in ApoE4 homozygotes 9.2%, compared with heterozygotes 1.7% and non-carriers 1.4%. Symptoms occurring in more than 1 subject were headache, confusional state, dizziness, and nausea.

The majority (81%) of ARIA-E resolved both clinically and radiographically by 4 months since onset and all 113 cases of ARIA-E in subjects treated with LEC10-BW resolved during the core period of study 301, with the exception of 1 subject that had residual headache. In 11% of subjects' resolution took more than 150 days.

The majority of subjects that experienced an event of ARIA-E (85% [96/113]) continued on lecanemab treatment with or without dose interruption (only subjects with asymptomatic radiographically mild ARIA-E could continue without dose interruption). Among those that continued lecanemab, recurrence of ARIA-E was common in ApoE4 non-carriers (9%) and very common in heterozygotes (15%) and homozygotes (54%). No apparent worsening in severity or resolution rates was observed with recurrent events.

Multiple analyses were performed to assess the impact of ARIA-E (and ARIA-H) on cognition and function. Whilst there are limitations to these data as they rely on hypotheses about the cognitive state of patients after ARIA (either by censoring or by imputation), results from these analyses consistently favoured LEC10-BW over placebo. Whilst the results based on imputation are slightly lower than those based on censoring, the treatment effects are in-line with what has been seen in other, conservative analyses. When incorporated in the primary MMRM model, ARIA was not a statistically significant covariate (static or time-varying). Individual subject plots have also been presented which show no clear pattern of adverse impact on cognition and function. Overall, these analyses provide some reassurance regarding ARIA and any potential adverse impact on cognition or function.

Whilst the analysis of ARIA-E in study 201 is limited by the different stopping rules which were more stringent than in study 301, and the lower percentage of ApoE4 carriers in LEC10 BW, overall similar trends to those in study 301 core were observed. In addition, a clear dose-response was observed with a higher incidence of ARIA-E in subjects receiving LEC10-M and LEC10-BW.

‘ARIA-E’ is included in the RMP as an important identified risk with further characterisation of this risk planned post-authorisation.

Lecanemab is not indicated for use in patients who are APOE E4 homozygotes

ARIA-H

ARIA-H can occur in 2 settings: 1) concurrent with ARIA-E and 2) isolated ARIA-H events not associated with ARIA-E. Throughout this section, macrohaemorrhage is used synonymously with intracerebral macrohaemorrhage.

Study 301 Core

Incidence

Table CS20: Treatment-emergent ARIA-H subcategories – Study 301 Core (SAS)

	Total		Isolated	
	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
ARIA-H (micro, macro, superficial)	81 (9.0)	155 (17.3)	70 (7.8)	80 (8.9)
Cerebral microhemorrhage	68 (7.6)	126 (14.0)	63 (7.0)	60 (6.7)
Superficial siderosis	21 (2.3)	50 (5.6)	13 (1.4)	23 (2.6)
Macrohemorrhage[a]	1 (0.1)	5 (0.6)	1 (0.1)	4 (0.4)
Symptomatic ARIA-H	2 (0.2)	13 (1.4)	2 (0.2)	4 (0.4)
ARIA-H by *APOE4* genotype				
APOE4 noncarrier, n/m (%)	12/286 (4.2)	33/278 (11.9)	11/286 (3.8)	23/278 (8.3)
APOE4 carrier, n/m (%)	69/611 (11.3)	122/620 (19.7)	59/611 (9.7)	57/620 (9.2)
APOE4 heterozygote, n/m (%)	41/478 (8.6)	67/479 (14.0)	35/478 (7.3)	40/479 (8.4)
APOE4 homozygote, n/m (%)	28/133 (21.1)	55/141 (39.0)	24/133 (18.0)	17/141 (12.1)

A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. A subject with two or more events is counted only once for that event. a: Incidence in this table is presented for TEAEs; considering not treatment emergent events, in Study 301 Core, the subtype of macrohaemorrhage (including not treatment emergent events) occurred in 2/897 subjects with PBO (0.2%) and 6/898 subjects with LEC10-BW (0.7%).

The incidence of ARIA-H leading to discontinuation of study drug was 0.1% in placebo and 1.7% in LEC10-BW. The incidence of ARIA–H leading to discontinuation of study drug in LEC10-BW was higher in ApoE4 carriers (14/620 [2.3%]) than in ApoE4 noncarriers (1/278 [0.4%]).

Table CS21: Serious TEAEs of ARIA-H Study 301 Core (SAS)

Treatment Group	Preferred Term or Subcategory	Isolated ARIA-H or Concurrent with ARIA-E	*APOE4* Carrier Status (Genotype)
LEC10-BW	Cerebral haemorrhage	Concurrent	Carrier (homozygous)
LEC10-BW	Amyloid related imaging abnormality-microhemorrhages and haemosiderin deposits	Concurrent	Noncarrier
LEC10-BW	Cerebral hemorrhage	Isolated	Carrier (heterozygous)
LEC10-BW	Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	Concurrent	Carrier (homozygous)
LEC10-BW	Cerebral hemorrhage	Isolated	Noncarrier
PBO	Hemorrhage intracranial	Isolated	Noncarrier

Timing

Isolated ARIA-H events occur throughout the course of treatment in placebo and LEC10-BW. The onset time of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E.

Radiographic severity

Table CS22: Maximum radiographic severity of ARIA-H - study 301 core (SAS)

	Placebo				**LEC10-BW**			
	Overall (n=897)	*APOE4 non carriers (n=286)*	*APOE4 heterozygotes (n=478)*	*APOE4 homozygotes (n=133)*	*Overall (n=898)*	*APOE4 non carriers (n=278)*	*APOE4 heterozygotes (n=479)*	*APOE4 homozygotes (n=141)*
Mild	73/897 (8.1%)	10/286 (3.5%)	39/478 (8.2%)	24/133 (18.0%)	97/898 (10.8%)	27/278 (9.7%)	48/479 (10.0%)	22/141 (15.6%)
Moderate	5/897 (0.6%)	0	1/478 (0.2%)	4/133 (3.0%)	26/898 (2.9%)	3/278 (1.1%)	9/479 (1.9%)	14/141 (9.9%)
Severe	3/897 (0.3%)	2/286 (0.7%)	1/478 (0.2%)	0	32/898 (3.6)	3/278 (1.1%)	10/479 (2.1%)	19/141 (13.5%)

Symptoms

Most ARIA-H was asymptomatic:

- Asymptomatic macrohaemorrhage: placebo 1/1 (100%; this event was fatal, although no prior symptoms were reported); LEC10-BW 3/5 (60%).
- Asymptomatic superficial siderosis: placebo 21/21 (100%); LEC10-BW 48/50 (96.0%).
- Asymptomatic cerebral microhaemorrhage: placebo 66/68 (97.1%); LEC10-BW 117/126 (92.9%).

Symptomatic ARIA-H was reported in 2/897 (0.2%) subjects in placebo and 13/898 (1.4%) subjects in LEC10-BW. The incidence of symptomatic ARIA-H was higher in ApoE4 homozygotes 3.5%, compared with heterozygotes 1% and non-carriers 1.1%. (respective incidence in placebo was 0.8%, 0.2% and 0%). Symptoms occurring in more than 1 subject in LEC10-BW were headache (4), dizziness (3), and confusional state (2).

Stabilisation

Unlike ARIA-E, ARIA-H does not resolve radiographically. Most ARIA-H in both placebo and LEC10-BW stabilized (PBO 77.8% [63/81], LEC10-BW 84.2% [128/152]) during the core period of the study. The remainder (both PBO and LEC10-BW) stabilized at first follow-up MRI or within 20 weeks for most subjects. There were no differences in stabilization of ARIA-H by ApoE4 status.

Recurrence

Among the patients who experienced an event of ARIA-H and continued on lecanemab with or without dose interruption, the rates of recurrence were very common: 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).

There is no apparent worsening in severity or resolution rates with recurrent events.

Study 201 Core

ARIA-H

Table CS23: Treatment-emergent ARIA-H by ApoE4 status – Study 201 Core (SAS)

ARIA Term	Placebo (N=245) n/m (%)	Lecanemab 2.5 mg/kg Biweekly (N=52) n/m (%)	Lecanemab 5 mg/kg Monthly (N=51) n/m (%)	Lecanemab 5 mg/kg Biweekly (N=92) n/m (%)	Lecanemab 10 mg/kg Monthly (N=253) n/m (%)	Lecanemab 10 mg/kg Biweekly (N=161) n/m (%)
ARIA-H	12 (4.9)	3 (5.8)	7 (13.7)	13 (14.1)	24 (9.5)	10 (6.2)
APOE4 noncarriers	3/71 (4.2)	0/14	1/11 (9.1)	0/8	2/28 (7.1)	4/112 (3.6)
APOE4 carriers	9/174 (5.2)	3/38 (7.9)	6/40 (15.0)	13/84 (15.5)	22/225 (9.8)	6/49 (12.2)
APOE4 heterozygous carriers	8/134 (6.0)	3/33 (9.1)	3/28 (10.7)	12/70 (17.1)	13/165 (7.9)	3/39 (7.7)
APOE4 homozygous carriers	1/40 (2.5)	0/5	3/12 (25.0)	1/14 (7.1)	9/60 (15.0)	3/10 (30.0)

A TEAE is defined as an AE that: emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline); or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment; or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. A subject with 2 or more AEs in that category is counted only once. ARIA-H = amyloid-related imaging abnormality-haemorrhage (collective term for cerebral microhaemorrhage, superficial siderosis, and macrohaemorrhage seen radiologically on MRI, and may be symptomatic or asymptomatic).

Two serious TEAEs due to ARIA-H (subtype, microhaemorrhages and hemosiderin deposits) were reported, both in the LEC10-BW group and both in ApoE4 carriers.

Most treatment-emergent ARIA-H (as cerebral microhaemorrhage) were radiographically mild in severity; with no subjects on placebo and 3 (0.5%) subjects in lecanemab groups (LEC10-BW 2 [1.2%]) reporting severe events. The single ARIA-H as macrohaemorrhage event (LEC10-BW 1 [0.6%]) was mild. All treatment-emergent ARIA-H (as superficial siderosis) were radiographically mild to moderate in severity.

Most ARIA-H was asymptomatic, with the time to onset of ARIA-H following the pattern of ARIA-E.

Pool LEC10-BW

The Pool LEC10-BW findings were similar to what was seen in Study 301 Core. Incidence of ARIA-H increased with the number of ApoE4 alleles.

Summary

In study 301 core, the overall incidence of treatment-emergent ARIA-H (including microhaemorrhage, superficial siderosis and macrohaemorrhage) was higher in the LEC10-BW group (17.3%) than placebo (9%). The higher incidence in the LEC10-BW group is mainly driven by concurrent ARIA-H and ARIA-E events with the timing of onset of these events following the pattern of ARIA-E. The incidence of ARIA-H with LEC10-BW and placebo was much higher in ApoE4 homozygous patients (39% vs 21.1%) compared with heterozygotes (14% vs 8.6%) and non-carriers (11.9% vs 4.2%).

The incidence of isolated ARIA-H events was similar in the LEC10-BW group compared with placebo (8.9% vs 7.8%) and these isolated events occurred throughout the course of treatment in placebo and LEC10-BW.

The incidence of serious events of ARIA-H was low (placebo 0.1%, LEC10-BW 0.6%). In patients treated with LEC10-BW, the incidence was highest in APOE4 homozygous patients (1.4%) compared with heterozygotes (0.2%) and non-carriers (0.79%).

Whilst the incidence of ARIA-H leading to discontinuation of study drug was low, these events occurred mainly in patients treated with LEC10-BW (1.7%) compared with placebo (0.1%).

Most treatment-emergent ARIA-H were radiographically mild to moderate in severity. The incidence of radiographically severe ARIA-H was higher with LEC10-BW (3.6% [20.6% of subjects that reported ARIA-H]) of subjects on LEC10-BW compared with placebo (0.3%), mostly driven by any microhaemorrhage event that resulted in a cumulative number greater than 10 microhaemorrhages. The rate of severe radiographic ARIA-H was highest in ApoE4 homozygotes 13.5%, compared to heterozygotes 2% or non-carriers 1%. The respective rates in the placebo group were 0%, 0.2% and 0.7%.

Most ARIA-H was asymptomatic. Symptomatic ARIA-H was reported in 1.4% of subjects on LEC10-BW and 0.2% of subjects on placebo. In the LEC10-BW group, the incidence of symptomatic ARIA-E was higher in ApoE4 homozygotes 3.5%, compared with heterozygotes 1% and non-carriers 1.1%. (respective incidence in placebo was 0.8%, 0.2% and 0%). Symptoms occurring in more than 1 subject in LEC10-BW were headache, dizziness, and confusional state.

Most ARIA-H in both placebo (77.8%) and LEC10-BW (84.2%) stabilised by the end of the Core period. The remainder stabilised at first follow-up MRI or within 20 weeks for most subjects. There were no differences in stabilisation of ARIA-H by ApoE4 status.

Following an initial event of ARIA-H, the rate of recurrence on resumption of treatment with LEC10-BW is very common in ApoE4 non-carriers (22%), heterozygotes (42%) and homozygotes (62%). The respective rates in the placebo group were 14%, 33% and 50%. No apparent worsening in severity or resolution rates was observed with recurrent events.

When considering events of intracerebral haemorrhage (ICH) in study 301 core, ICH greater than 1cm was reported in 6 (0.7%) subjects on LEC10-BW and 2 (0.2%) on placebo, of which 5 and 1 case respectively were treatment emergent. Of the treatment-emergent events, 3 in the LEC10-BW and 1 in placebo were serious adverse events. All cases of ICH>1cm were ongoing at the end of the core study.

Including all LEC10-BW exposures in Study 301 Core and OLE phase combined, there were 11/1616 (0.7%) ICH > 1 cm reported. This includes 2 deaths in the OLE phase with concurrent ICH>1 cm.

Risk factors for ICH with lecanemab include i) concomitant use of anticoagulants or a thrombolytic agent, ii) the presence of an ApoE4 allele (particularly homozygotes) as this is associated with more severe cerebral amyloid angiopathy (CAA) which has an increased risk for ICH, iii) findings on MRI that indicate an increased risk for ICH including findings suggestive of CAA or other lesions (e.g. aneurysm, vascular malformation), and iv) a bleeding disorder that is not under adequate control. Appropriate contraindication and warnings to address these risk factors are included in the SmPC. Lecanemab is not indicated for use in patients who are ApoE4 homozygotes.

In study 201 core, whilst the overall incidence of ARIA-H was higher in lecanemab groups compared with placebo, the rates were lower than those observed in study 301 core (both placebo and lecanemab). This likely reflects the more stringent stopping rules and the lower percentage of ApoE4 carriers in LEC10 BW in study 201. Otherwise, similar overall trends to those in study 301 core were observed. There was one report of cerebral macrohaemorrhage reported in study 201 core. This occurred in the LEC10-BW group, was radiographically mild and the subject was an ApoE4 non-carrier.

'ARIA-H (cerebral microhaemorrhage and superficial siderosis) and intracerebral haemorrhage greater than 1cm (i.e. microhaemorrhage)' are included as important identified risks in the RMP.

ARIA-H (microhaemorrhage and superficial siderosis) and intracerebral haemorrhage and Antithrombotic use

Table CS24: ARIA incidence and concurrent antiplatelet or anticoagulant use – Study 301 Core (SAS)

	ARIA-H (MH or SS)		Intracerebral Haemorrhage	
	PBO	LEC10-BW	PBO	LEC10-BW
Not on antiplatelet or anticoagulation at any time	49/586 (8.4%)	93/564 (16.5%)	1[a]/586 (0.2%)	3/564 (0.5%)
Event post any antiplatelet (aspirin or non-aspirin)	22/237 (9.3%)	40/251 (15.9%)	1/237 (0.4%)	1/251 (0.4%)
Event post dual aspirin and non-aspirin	2/19 (10.5%)	3/20 (15.0%)	0/19 (0%)	0/20 (0%)
Event post any anticoagulation (alone or with antiplatelet)	7/74 (9.5%)	9/83 (10.8%)	0/74 (0%)	2[a]/83 (2.4%)
Event post dual antiplatelet + anticoagulation	0/21 (0%)	4/35 (11.4%)	0/21 (0%)	1/35 (2.9%)

a: indicates 2 intracerebral haemorrhage events [1: LEC10-BW, 1: PBO], which occurred >30 days after last dose

In study 301, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was permitted if the subject was on a stable dose.

The concomitant use of antithrombotic medication in study 301 core was similar between LEC10-BW (35.5%) and placebo (33.2%). The most commonly used antithrombotic medication was aspirin (LEC10-BW 26.8%; placebo 26.8%) accounting for 75% of the exposures to antithrombotic medication, followed by clopidogrel (LEC10-BW 4.5%; placebo 3.2%) and apixaban (LEC10-BW 3.5%; placebo 3.2%). Other individual antithrombotic agents were each used by less than 1.8% of the subjects in both the groups, and use was balanced between LEC10-BW and placebo.

Based on the analysis in the table above, aspirin and other antiplatelet agents were used in the trial with no increase in the risk of ARIA-H or intracerebral haemorrhage with lecanemab.

Whilst the exposure to anticoagulants in the placebo-controlled trial is limited and the number of events is small, there was a numerical imbalance in the incidence of intracerebral haemorrhage in lecanemab patients receiving anticoagulation (alone or with an antiplatelet agent) 2.4% (2/83) and those on no antiplatelets or anticoagulation 0.5% (3/564) or antiplatelets only 0.4% (1/251).

In Study 301 OLE phase there was a fatal report of tPA administration concomitant with LEC10-BW, which resulted in multiple intracerebral haemorrhages. 'Intracerebral haemorrhage' is a common adverse event for tPA.

Summary

Aspirin and other antiplatelet agents were used in study 301 core with no increase in the risk of ARIA-H or intracerebral haemorrhage with lecanemab.

Whilst the numbers are very low, fatal events of intracerebral haemorrhage have been observed in patients taking lecanemab. Anticoagulation increases the risk of haemorrhage and there is a biologically plausible potential increased risk of intracerebral haemorrhage with concomitant use of lecanemab and anticoagulants or thrombolytic agents (e.g. tPA).

Although the exposure to anticoagulants in study 301 core was limited and the number of events is small, there was a numerical imbalance in the incidence of intracerebral haemorrhage in lecanemab patients receiving anticoagulation (alone or with an antiplatelet agent) 2.4% (2/83) and those on no antiplatelets or anticoagulation 0.5% (3/564) or antiplatelets only 0.4% (1/251).

An appropriate contraindication and warnings regarding the use of lecanemab in patients receiving anticoagulant therapy or thrombolytic agents are included in the SmPC.

Skin rash and other hypersensitivity reactions related to study drug
See adverse events section above.

Suicidal behaviour and ideation
The potential for lecanemab to precipitate suicidal thoughts and behaviour was assessed using the validated Columbia Suicide Severity Rating Scale (C-SSRS). In study 301 Core and 201 Core, the incidence of postbaseline suicidal ideation of various grades was similar between lecanemab and placebo; there were no dose-related trends on lecanemab (Study 201 only). There were no Grades 4 and 5 suicidal ideations reported in any study. Similar results were observed in Pool Core and Pool LEC10-BW analyses. One subject on lecanemab in study 301 core attempted suicide.

Laboratory findings
Overall, in Study 201 Core and Study 301 Core there were no clinically meaningful effects of lecanemab on clinical laboratory parameters (chemistry, haematology, and urinalysis) over time, and there were no dose-related trends. There were no shifts from Baseline of clinical concern, and the pattern of shifts was similar across treatment groups.

In study 201 core there was a dose dependent reduction in lymphocyte count and increase in

neutrophil counts in those receiving lecanemab compared to placebo occurring a few hours after the first infusion. Lymphocyte and neutrophil counts were not obtained after the 1st infusion in study 301 core. These transient changes are likely due to infusion related reaction. The majority of the participants did not have persistent changes in lymphocyte or neutrophil counts, and there were no clinically significant adverse events, such as infections associated with these changes.

Within the entire lecanemab program, there was 1 case of Hy's Law in a subject that received placebo in Study 301 Core with aetiology of herbal medicines.

The analysis of laboratory parameters in Study 301 Core and OLE Phase are consistent with what was reported in Study 201 Core and OLE Phase and are consistent across Pool Core and Pool LEC10-BW.

Vital signs, physical findings and other observations related to safety

Vital signs
In Study 301, Study 201, Pool Core, and Pool LEC10-BW there were no clinically meaningful effects of lecanemab on vital signs over time and there were no dose-related trends (Study 201 Core only). Overall, the incidence of notably abnormal vital signs was low and similar across treatment groups. In study 301 Core the incidence of clinically notable high temperature (>38.0°C) at Week 1 post first dose was lower in placebo (0%) than LEC10-BW (0.7%). A similar trend was observed for high pulse rate (placebo 0%; LEC10-BW 1.8%). These rates are low, only observed post dose, and are considered to be part of an infusion-related reaction. Similar results were observed in study 201 core affecting the higher doses of lecanemab (LEC5 BW, LEC10 M, and LEC10-BW).

Electrocardiograms
There were no clinically meaningful effects of lecanemab on ECG parameters over time, and there were no shifts from Baseline of clinical concern and no dose-related trends (Study 201 only). The incidence of abnormal ECG parameters was low and similar across treatment groups.

Safety in special populations
Study 301 Core represents the largest dataset that is balanced for randomisation strata and has sufficient number of subjects in most of the intrinsic and extrinsic factors analysed. Therefore, the presentation of results in this section is for Study 301 Core only.

Subgroup analyses of TEAES and AESI in study 301 core

More than 80% of subjects in the safety population in study 301 Core were ≥65 years of age. All treatment-emergent deaths on both placebo and lecanemab occurred in this age group. Whilst there was a higher rate of SAEs and TEAEs leading to study drug dose discontinuation in this age group, this trend was seen in both the placebo and lecanemab groups.

Most subjects were White (77%) with 17% Asian and 3% Black or African American. All treatment-emergent deaths occurred in White subjects. A lower incidence of TEAEs leading to study drug dose discontinuation was reported in Asian and Black or African American subjects compared with White subjects.

The incidence of infusion-related reaction with lecanemab was lower in Asians and Black or African American subjects compared to White subjects. This observation was also seen in subjects on placebo.

The incidence of ARIA-E with lecanemab was lower in Asians and Black or African American subjects than White subjects. In both the placebo and lecanemab groups the incidence of ARIA-H was higher in subjects ≥65 years than in subjects <65 years. As described in the AESI section above, a clinically relevant difference in the incidence and severity of ARIA events is seen according to ApoE4 status.

Immunological events

In study 301 core, postbaseline 5.5% of subjects were treatment-emergent ADA positive, 48.5% were ADA negative conclusive, and 45.9% were ADA negative inconclusive. Titers were generally low and tended to decrease with longer duration of dosing. Of the subjects with ADA, few had neutralising antibodies (2 subjects).

In study 201 core, postbaseline 40.9% of subjects were treatment-emergent ADA positive in the LEC10-BW group with low titers. The incidence of treatment-emergent Nab was 25.4%, with low titers.

In study 301 core, overall TEAE rates and incidence of IRRs was similar between ADA positive and ADA negative conclusive subjects. IRR rates were slightly lower in ADA negative inconclusive subjects.

The current bioanalytical method for ADAs has a limited drug tolerance level of 31.3 µg/mL for lecanemab. The applicant has advised that a more sensitive ADA assay with an increased drug tolerance is currently in development. The applicant is proposing to submit a reanalysis of the samples from study 301 core in late 2025. Provision of this new data, together with a re-evaluation of any impact of immunogenicity on efficacy, safety and PK is a post-authorisation commitment.

Safety related to drug-drug interactions and other interactions

Lecanemab is a mAb that targets aggregated soluble and insoluble forms of Aβ and is not expected to be involved in cytokine modulated pathways. Elimination of lecanemab occurs 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, pharmacokinetic drug interactions with concomitantly administered agents. For these reasons, no specific clinical or nonclinical drug-drug interaction studies have been conducted for lecanemab and none are planned.

In Study 301 and Study 201, concomitant approved symptomatic AD treatments were allowed. The incidence and type of TEAEs for LEC10-BW and placebo was similar in subjects with and without concomitant approved symptomatic AD treatment.

Intracerebral haemorrhage is a recognised adverse reaction with lecanemab treatment. The potential for an increased risk of intracerebral haemorrhage with concomitant antithrombotic medication is considered above.

Discontinuation due to adverse events

Study 301 Core

Table CS25: TEAEs leading to discontinuation of study drug by SOC and PT occurring in ≥2 subjects in any treatment group – Study 301 Core (SAS)

MedDRA System Organ Class Preferred Term	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
Subjects with any TEAE leading to discontinuation from study drug	28 (3.1)	64 (7.1)
Cardiac disorders		
Myocardial infarction	2 (0.2)	1 (0.1)
Injury, poisoning and procedural complications		
Infusion-related reaction	1 (0.1)	12 (1.3)
Subdural hematoma	2 (0.2)	1 (0.1)
Nervous system disorders		
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	1 (0.1)	15 (1.7)
Amyloid related imaging abnormality-oedema/effusion	0	14 (1.6)
Superficial siderosis of central nervous system	0	4 (0.4)
Psychiatric disorders		
Depression	0	2 (0.2)

Excluding discontinuations due to events of infusion-related reactions, ARIA-E, and ARIA-H, the incidence of TEAEs leading to discontinuation of study drug was similar between placebo (2.9%) and LEC10-BW (3.2%).

Study 201 Core

The incidence of TEAEs leading to discontinuation of study drug was lower in placebo (5.7%) than the lecanemab treatment groups (LEC2.5-BW [13.5%], LEC5-M [7.8%], LEC5-BW [10.9%], LEC10-M [18.6%], and LEC10-BW [14.9%]). Excluding discontinuations due to events of ARIA-E, the incidence of TEAEs leading to discontinuation of study drug in LEC10-BW was approximately 5%.

Pool LEC10-BW

Similar to Study 301 Core, the incidence of TEAEs leading to study drug discontinuation was 7.0%. The most common (≥5 subjects in any treatment group) TEAEs leading to discontinuation were similar to Study 301 Core and included ARIA-E (2.2%), infusion related reaction (1.4%), amyloid related imaging abnormality-microhaemorrhages and hemosiderin deposits (1.1%), and superficial siderosis of central nervous system (0.4%) 6.11.2.

TEAEs resulting in study drug dose interruption or infusion interruption

Study 301 Core

The incidence of TEAEs leading to study drug dose interruption was lower in placebo (7.9%) than LEC10-BW (19.5%). Excluding events of IRRs, ARIA-E, ARIA-H, the incidence of

TEAEs leading to study drug dose interruption were 6.6% in placebo and 10% in LEC10-BW.

The most common (≥5 subjects in either placebo or LEC10-BW) TEAEs leading to study drug dose interruption included:
• Placebo: COVID-19 (1.1%), infusion site extravasation (0.8%), IRR (0.7%), ARIA-E (0.7%), atrial fibrillation (0.7%).
• LEC10-BW: ARIA-E (7.8%), amyloid related imaging abnormality-microhaemorrhages and hemosiderin deposits (a preferred term for cerebral microhaemorrhage) (3.9%), infusion-related reaction (1.4%), superficial siderosis of central nervous system (1.4%), COVID-19 (1.1%), infusion site extravasation (1.0%), headache (0.8%).

TEAEs leading to infusion interruption were reported in 1.2% of subjects in the placebo group and 2.4% LEC10-BW. Excluding events of IRRs, ARIA-E, ARIA-H, incidence of TEAEs leading to infusion interruption was similar between placebo (1.1%) and LEC10-BW (1.4%). The most common (≥5 subjects in either PBO or LEC10-BW) TEAEs leading to infusion interruption were: Placebo: Infusion site extravasation (0.7%); LEC10-BW: Infusion-related reactions (0.9%), infusion site extravasation (0.8%).

Study 201 Core
The incidence of TEAEs leading to study drug dose interruption was balanced with no dose-related trends (placebo 14.7%, LEC2.5-BW 15.4%, LEC5-M 9.8%, LEC5-BW 16.3%, LEC10-M 7.9%, and LEC10-BW 11.8%). TEAEs that resulted in study drug interruption in more than 1 subject in LEC10-BW were infusion site extravasation (1.2%) and herpes zoster (1.2%).

A low incidence was also reported for TEAEs leading to infusion interruption (placebo 2.4%, LEC2.5-BW 5.8%, LEC5-M 3.9%, LEC5-BW 5.4%, LEC10-M 1.6%, and LEC10-BW 1.2%). TEAEs that resulted in infusion interruption in more than 1 subject in the LEC10-BW group was infusion site extravasation (1.2%).

Pool LEC10-BW
The overall incidence of TEAEs leading to study drug dose interruption or infusion interruption was low and was similar to that reported in Study 301 Core.

Summary
Discontinuation of study drug:
The incidence of TEAEs leading to discontinuation of study drug was higher in subjects receiving LEC10-BW compared to placebo in both study 301 core (7.1% vs 3.1%) and study 201 core (14.9% vs 5.7%).

The most frequent events resulting in lecanemab discontinuation and at greater frequency than placebo were ARIA-H, ARIA-E, and infusion related reactions. In both studies, when these events were excluded, the incidence of TEAEs leading to discontinuation of study drug was similar between the LEC10-BW groups and placebo.

The higher incidence of TEAEs leading to discontinuation in the LEC10-BW group in study 201 core compared with 301 is not unexpected due to the protocol required discontinuations for ARIA-E regardless of severity in study 201 core (in study 301 core subjects with asymptomatic and radiographically mild ARIA-E at onset were permitted to continue dosing).

Study drug dose interruption or infusion interruption:
In study 301 core, the incidence of TEAEs leading to study drug dose interruption was higher in the LEC10-BW (19.5%) group than placebo (7.9%), mainly due to higher rates of IRRs, ARIA-E and ARIA-H. In study 201 core, the incidence in the LEC10-BW group was lower (11.8%) and similar to placebo (14.7%), likely reflecting the difference in the study protocol in terms of ARIA-E events.

The incidence of TEAEs leading to infusion interruption was low in both studies.

Post marketing experience

Lecanemab was approved in the United States of America (US) on 06 Jan 2023 via the accelerated approval pathway and received traditional approval in the US on 06 Jul 2023. Cumulative through 29 Feb 2024, there have been approximately 3000 patients treated in the US.

As of 29 Feb 2024, there have been post-marketing reports of AEs in 331 patients who experienced 794 AEs. Excluding reports of ARIA which are further described below, the most commonly reported AEs include headache (88 events), fatigue (40 events), chills (39 events), confusional state (30 events), pyrexia (29 events), nausea (24 events), dizziness (22 events) and infusion related reaction (16 events). The majority of these events were reported following the 1st or 2nd infusion of lecanemab and considering the timing and presentation these events are largely consistent with the types of infusion related reactions seen in the clinical development program.

During the same reporting period, serious adverse events have been reported in 41 patients who experienced 71 SAEs. Most fell in the SOCs of nervous system disorders and infections and infestations and were generally consistent with those observed during the clinical development program and for the population being treated. Three of the SAEs were fatal, 2 of which were not considered related to treatment (fall and progression of AD; myocardial infarction in a patient with significant risk factors). The 3rd report relates to an ApoE4 homozygous patient who developed severe ARIA-E, severe ARIA-H (microhaemorrhage) and moderate superficial siderosis 6 weeks after starting lecanemab. The cause of death was not known but was considered possibly related to lecanemab by the reporter.

There have been reports of 43 patients who experienced 55 ARIA or potential ARIA events which are described in the table below.

Table CS26: Summary of Postmarketing Reports of ARIA as of 29 Feb 2024

Preferred Terms	Non-Serious Events	Serious Events	Total Events	Fatal Events
Amyloid related imaging abnormalities	4	3	7	0
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	17	4	21	0
Amyloid related imaging abnormality-oedema/effusion	12	4	16	0
Brain oedema	3	2	5	0
Cerebral haemorrhage	3	1	4	0
Cerebral microhaemorrhage	1	0	1	0
Superficial siderosis of central nervous system	1	0	1	0
Total Events	**41**	**14**	**55**	**0**

The 4 reports of cerebral haemorrhage are non-serious consumer reports, 3 of which reported a verbatim term of "brain bleeding" or "bleeding in the brain," which have not been medically confirmed. The 4th report is a serious consumer report describing a patient who was hospitalised with chest pain within the first week of lecanemab therapy and during hospitalization the patient developed a cerebral haemorrhage.

One serious health professional report of brain oedema is unlikely to represent ARIA as it was noted to have been the result of trauma when a patient tripped and fell on the way to the bathroom.

Summary
Overall, the adverse events reported since lecanemab was approved in the US are consistent with the safety profile observed in the clinical development programme.

In-line with what was observed in the clinical trials, reports of ARIA related to lecanemab generally occurred early in treatment and the majority of cases were non-serious. In many of the serious reports provided, the data provided by the reporter was limited, hampering any conclusions that can be drawn. Up to 29 February 2024, one fatal case of ARIA has been reported in the post-marketing setting in an ApoE4 heterozygous patient.

Discussion on clinical safety

Across the clinical development programme, in total 2203 subjects have received at least one dose of lecanemab.

The main safety data in support of the use of lecanemab 10mg/kg biweekly in the intended patient population (early Alzheimer's disease) are from studies 201 and 301. In the completed placebo-controlled periods of these studies, 1059 subjects received at least one dose of LEC10-BW of which 917, 854 and 589 were exposed for ≥6, ≥12 and ≥18 months respectively.

Longer term uncontrolled safety data with LEC10-BW is available from the ongoing open label extension phases of these studies with 505 subjects receiving LEC10-BW for at least 24 months and 47 subjects receiving LEC10-BW for at least 36 months in study 301 OLE and 124 subjects receiving LEC10-BW for at least 24 months and 92 subjects receiving LEC10-BW for at least 36 months in study 201 OLE.

Post-marketing safety data is also available from the US where approximately 3000 patients had received lecanemab up to 29 February 2024.

Consistent with the known safety profile of other monoclonal antibodies directed against aggregated forms of beta amyloid, the main risks associated with lecanemab in patients with early Alzheimer's disease are infusion related reactions, amyloid related imaging abnormalities and cerebral haemorrhage.

Infusion related reactions were very common in subjects treated with lecanemab (26% vs 7% with placebo in study 301 core). The majority of infusion reactions were mild to moderate in severity and occurred with the first infusion. Severe infusion-related reactions were reported in less than 1% patients, most of which occurred during the infusion or within 2.5 hours after infusion completion. The incidences of skin rash and other hypersensitivity

reactions in study 301 were low. A case of anaphylaxis was also reported. These reactions are considered monitorable and manageable. Appropriate warnings and precautions have been included in the product information.

ARIA-E was very common in subjects treated with lecanemab (13% vs 2% with placebo in study 301 core). Most events occurred within the first 3 months of treatment in the lecanemab group, with the majority (81%) resolving within 4 months. The majority of events were asymptomatic, with symptomatic ARIA-E occurring in 3% of lecanemab subjects. The incidence of serious adverse events of ARIA-E was low (0.7%). Among the patients who experienced an event of ARIA-E and continued on lecanemab with or without dose interruption, the rates of recurrence were very common.

ARIA-H was very common in subjects treated with lecanemab (17% vs 9% in placebo in study 301 core). There was no increase in isolated ARIA-H (i.e., in subjects who did not also experience ARIA-E) compared to placebo. The onset time and distributions, of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E while isolated ARIA-H occurred throughout the course of treatment. ARIA-H stabilised in 84% of patients treated with lecanemab compared with 78% patients on placebo by the end of the core period of study 301. The remainder stabilised at first follow-up MRI or within 20 weeks for most subjects. Among the patients who experienced an event of ARIA-E and continued on lecanemab with or without dose interruption, the rates of recurrence were very common.

Intracerebral haemorrhage > 1cm was uncommon in subjects treated with lecanemab. In study 301 core, ICH was reported in 6 (0.7%) subjects on LEC10-BW and 2 (0.2%) on placebo, of which 5 and 1 case respectively were treatment emergent. Of the treatment-emergent events, 3 in the LEC10-BW and 1 in placebo were serious adverse events. All cases of ICH>1cm were ongoing at the end of the core study. Including all LEC10-BW exposures in Study 301 Core and OLE phase combined, there were 11/1616 (0.7%) intracerebral haemorrhage > 1 cm reported. This includes 2 deaths in the OLE phase with concurrent ICH>1 cm. There was one report of ICH>1cm in study 201 core that was mild and occurred in the LEC10-BW group.

Approximately 15% of Alzheimer's disease patients are ApoE4 homozygotes. Homozygous patients have a higher prevalence and severity of cerebral amyloid angiopathy. 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. Lecanemab is not indicated for use in patients who are homozygotes.

Table CS27: Incidence of key ARIA events in study 301 core in the overall population and by ApoE4 status

	Placebo				**Lecanemab**			
	Overall n=897	**Non-carrier n=286**	**Heterozygote n=478**	**Homozygote n=133**	**Overall n=898**	**Non-carrier n=278**	**Heterozygote n=479**	**Homozygote n=141**
ARIA-E	**1.7% (15/897)**	**0.3% (1/286)**	**1.9% (9/478)**	**3.8% (5/133)**	**12.6% (113/898)**	**5.4% (15/278)**	**10.9% (52/479)**	**32.6% (46/141)**
Symptomatic ARIA-E	0%	0%	0%	0%	2.8% (25/898)	1.4% (4/278)	1.7% (8/479)	9.2% (13/141)
Severe radiographic ARIA-E	0%	0%	0%	0%	1.0% (9/898)	0%	0.4% (2/479)	5.0% (7/141)
Serious ARIA-E	0%	0%	0%	0%	0.8% (7/898)	0.7% (2/278)	0.4% (2/479)	2.1% (3/141)
ARIA-H*	**8.9% (80/897)**	**3.8% (11/286)**	**8.6% (41/478)**	**21.1% (28/133)**	**16.9% (152/898)**	**11.5% (32/278)**	**13.8% (66/479)**	**38.3% (54/141)**
Symptomatic ARIA-H	0.2% (2/897)	0%	0.2% (1/478)	0.8% (1/133)	1.4% (13/898)	1.1% (3/278)	1.0% (5/479)	3.5% (5/141)
Severe radiographic ARIA-H	0.3% (3/897)	0.7% (2/286)	0.2% (1/478)	0%	3.6% (32/898)	1.1% (3/278)	2.1% (10/479)	13.5% (19/141)
Serious ARIA-H	0.1% (1/897)	0.3% (1/286)	0%	0%	0.6% (5/898)	0.7% (2/278)	0.2% (1/479)	1.4% (2/141)
Intracerebral haemorrhage >1cm	**0.1% (1/897)**	**0.3% (1/286)**	**0**	**0**	**0.7% (6/898)**	**0.4% (1/278)**	**0.6% (3/479)**	**1.4% (2/141)**

*Total ARIA-H (Isolated ARIA-H and ARIA-H in association with ARIA-E)

Cerebral amyloid angiopathy is present pathologically in almost all AD cases, but most patients show no imaging findings or clinical manifestations. The presence and severity of CAA is impacted by ApoE4 status. Patients were excluded from enrolment in the clinical trials for lecanemab if they had findings suggestive of cerebral amyloid angiopathy (prior cerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema) on their baseline MRI scan due to the increased risk of ARIA and intracerebral haemorrhage. A recent brain MRI is required before initiating treatment with lecanemab and use is contraindicated in patients if any of the above findings suggestive of CAA are present.

Aspirin and other antiplatelet agents were used in study 301 core with no increase in the risk of ARIA-H or intracerebral haemorrhage with lecanemab.

Anticoagulation increases the risk of haemorrhage and there is a biologically plausible potential increased risk of intracerebral haemorrhage with concomitant use of lecanemab and anticoagulants or thrombolytic agents (e.g. tPA). Although the exposure to anticoagulants in study 301 core was limited and the number of events is small, there was a numerical imbalance in the incidence of intracerebral haemorrhage in lecanemab patients receiving anticoagulation (alone or with an antiplatelet agent) and those on no antiplatelets or anticoagulation or antiplatelets. Initiation of treatment with lecanemab is contraindicated in patients receiving ongoing anticoagulant therapy and there are appropriate warnings in the SmPC regarding administration of anticoagulants or a thrombolytic agent to a patient already being treated with lecanemab.

Clear guidance is provided in the SmPC regarding clinical and MRI monitoring for ARIA and recommendations for when dosing should be suspended or permanently discontinued following an event or ARIA including ICH.

In the placebo controlled clinical trials, the safety profile after the first 6 months of treatment was similar in the LEC10-BW and PBO treated patients.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended.

The important identified risks, important potential risks and missing information for Leqembi are as follows:

Table RMP 1: Summary of important risks and missing information for Leqembi.

Important identified risks	• Amyloid-related imaging abnormalities - oedema/effusion (ARIA-E) • Amyloid-related imaging abnormalities - haemosiderin deposition (ARIA-H [cerebral microhaemorrhage and superficial siderosis]) • Amyloid-related imaging abnormalities (ARIA) intracerebral haemorrhage greater than 1 cm in diameter
Important potential risks	None
Missing information	• Accelerated brain volume loss • Long-term safety

In addition to routine pharmacovigilance measures, the following additional pharmacovigilance measures have been proposed:

Table RMP 2: Summary of ongoing and planned additional pharmacovigilance activities.

Study name and description (status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates

Category 1: Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
PASS (planned)	Characterise the long-term safety, collect available effectiveness data, and provide GB serious ARIA/ICH reporting rates to evaluate the effectiveness of the educational materials.	• Long-term safety • ARIA-E • ARIA-H • ARIA intracerebral haemorrhage > 1 cm in diameter	Draft protocol	Within 6 months of approval
			Final protocol	Within 15 months of approval
			Progress reports	Aligned to PSUR cycle
			Final report	To be determined
Category 2: Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3: Required pharmacovigilance activities				
Study 301 open-label extension (ongoing)	Evaluate the long-term safety of lecanemab in subjects with early AD.	Long-term safety	Progress reports	March 2026
			Final report	2030
Study 303 (ongoing)	Evaluate efficacy and safety of lecanemab in the preclinical AD population.	Accelerated brain volume loss	Final report	February 2030

Key: AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormalities oedema/effusion; ARIA-H = amyloid-related imaging abnormalities- haemosiderin deposition (cerebral microhaemorrhage and superficial siderosis); GB = Great Britain; PASS = post authorisation safety study; PSUR = periodic safety update report.

In addition to routine risk minimisation measures, the following additional risk minimisation measures have been proposed to mitigate the risks of ARIA-E, ARIA-H and ARIA intracerebral haemorrhage > 1cm in diameter:

- Patient alert card
- Healthcare professional guide

A controlled access programme will also be implemented before Leqembi is launched to promote the safe and effective use of lecanemab in routine clinical practice. This programme will also characterise drug utilisation and off-label use.

IV.7 Discussion on the clinical aspects

Alzheimer's disease is an area of high unmet medical need. Current approved therapeutic agents are limited to symptomatic therapies. These therapies provide modest or temporary benefit to symptoms, which is rapidly lost after treatment discontinuation.

Lecanemab is a humanised IgG1 monoclonal antibody 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.

When taken in the context of the high burden Alzheimer's disease imposes on patients and their carers, the urgent high unmet medical need for effective treatments, and the benefits of reducing clinical decline, particularly at the early stage of disease when symptoms are still manageable and quality of life relatively preserved, it is considered that the efficacy results from the 18-month placebo-controlled period of pivotal study 301 core in the overall population are clinically meaningful and some reassurance regarding the reproducibility of these results is provided from study 201 core. However, whilst clinically meaningful, the overall benefits remain modest.

The adverse reactions of most concern with lecanemab treatment are ARIA-E, ARIA-H and intracerebral haemorrhage >1cm.

Approximately 15% of Alzheimer's disease patients are ApoE4 homozygotes. There are greater uncertainties around the magnitude of benefit in ApoE4 homozygous patients. Furthermore, 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. Currently there are insufficient data to infer a positive benefit-risk balance in ApoE4 homozygous patients.

Overall, the totality of data is considered to support a positive benefit-risk balance 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.

Use of lecanemab is contraindicated in the following patient populations:

- 'Hypersensitivity to the active substance or any of the excipients'. This is a standard contraindication with all medicinal products.

- '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).' This is due to the increased risk of ARIA and ICH in these patients who were excluded from the clinical trials.

- 'Treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy.' This is due to a biologically plausible potential increased risk of intracerebral haemorrhage with concomitant use of lecanemab and anticoagulants or thrombolytic agents, in the absence of sufficient clinical data to provide reassurance on the safety of such use.

Routine and additional pharmacovigilance and risk management measures have been agreed for lecanemab including a patient alert card, educational materials for healthcare professionals, a controlled access programme and an imposed post authorisation safety study.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in 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.

For products authorised with conditions

Leqembi 100 mg/ml concentrate for solution for infusion has been authorised with the condition to perform further studies and to provide additional measures to minimise its risks. The Marketing Authorisation Holder (MAH) shall complete, within the stated timeframe, the following measures:

Description	Due date
A. <u>KEY MEASURES IN THE RISK MANAGEMENT SYSTEM</u> **<u>Additional risk minimisation measures</u>**	
1. Imposed UK Lecanemab controlled access programme	
a. 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. The central registration system must cover the entire geographic area within the scope of the licence, include both National Health Service and independent sector prescribing and collect appropriate and relevant information on the specified data fields prior to the first infusion of lecanemab, for all patients which is to be agreed with the regulatory authority. b. This system is an additional risk minimisation measure to ensure the safe and effective use of lecanemab in routine clinical practice and to encourage healthcare professionals to consider the licensed indications and the benefit-risk profile in relevant subgroups. c. The platform should allow and encourage submission of follow up data on adverse events by prescribers. d. Submission of this follow up data should be encouraged, with reporting of adverse events in line with Good Pharmacovigilance Practice requirements. e. The data collected in the central registration system should be used to characterise off-label use and drug utilisation across subgroups.	To be implemented before product launch. Progress reports: submission dates aligned to periodic safety update report cycle.

f. The controlled access programme must be implemented prior to product launch in Great Britain and interim evaluation reports should be submitted in periodic safety update reports (PSURs), including aggregated summaries of drug utilisation across subgroups. g. The design and implementation of the central registration system must be agreed with the Medicines & Healthcare products Regulatory Agency (MHRA) before it is operationalised	
2. Educational materials	
Additional risk minimisation measures are required to mitigate the risks of amyloid-related imaging abnormalities (ARIAs) and intracerebral haemorrhage, including management advice for emergency care providers. The Marketing Authorisation Holder (MAH) should submit draft versions of the educational materials with a distribution plan to the MHRA for review and approval before Leqembi is marketed in the United Kingdom. The MAH should ensure that all healthcare professionals who are expected to prescribe or monitor lecanemab have access to/are provided with the following educational programme: • The summary of product characteristics • A healthcare professional guide • A patient alert card. The materials should include the key elements contained in Annex 6 of the risk management plan.	To be implemented before product launch.

B. CONDUCT POST AUTHORISATION SAFETY STUDIES	
3. Imposed post authorisation safety study (category 1)	
To investigate the safety and benefit-risk profile of lecanemab in routine clinical practice in the geography covered by the licence, particularly in relation to the incidence and severity of ARIAs and intracerebral haemorrhage, and long-term safety, a post authorisation safety study is imposed. The study should address the following aims: a. Quantify the incidence of known adverse events (including though not necessarily limited to anaphylaxis, ARIA-oedema [ARIA-E], ARIA-haemosiderin deposition [ARIA-H], and intracerebral haemorrhage), characterise the severity of these adverse events in real world use, and evaluate the association between these adverse events and relevant covariates including but not limited to apolipoprotein E ε4 (ApoE4) genotypes, concomitant antithrombotic therapy (including antiplatelet therapy, anticoagulant therapy, and thrombolytic therapy), and comorbid cerebral amyloid angiopathy. b. Identify previously unknown adverse events not identified in the clinical development programme – long-term safety. c. Characterise the benefit-risk profile in routine practice across patient subgroups, including but not necessarily limited to, ApoE4 genotypes, concomitant antithrombotic therapy (see above), and comorbid cerebral amyloid angiopathy. d. Determine the effectiveness of risk minimisation measures and identify barriers to their implementation The choice of study design should be made to minimise the incidence of missing data and identify and control sources of bias. Such a design could include primary data collection in a registry, an active surveillance study in recruited sites, or could make secondary use of existing healthcare data available from an academic registry for example. In designing the study, the MAH should take all reasonable steps to ensure the study accrues a representative sample of the patients exposed to the drug in real-world clinical practice, including though not limited to, the geographical regions in which patients are treated, the range of care settings in which patients are treated, and baseline characteristics of patients. Additionally, the MAH should ensure that the study is adequately powered to address the scientific objectives. Patients should be followed up for at least 6 months after discontinuation of lecanemab or for a minimum of 3 years, whichever is sooner. Reasons for loss to follow up should be captured wherever possible. Where possible, safety outcomes should be compared to an appropriate comparator group.	Study protocol submission: within 6 months of approval. Progress reports: submission dates aligned to periodic safety update report cycle. Final report: date to be determined.

A study protocol should be submitted for approval to the MHRA within 6 months of the date of the marketing authorisation.	

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PILs for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N