Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Kisunla 350 mg concentrate for solution for infusion

donanemab

PLGB 14895/0338

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LAY SUMMARY

Kisunla 350mg Concentrate for solution for infusion
donanemab

This is a summary of the Public Assessment Report (PAR) for Kisunla 350 mg 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 Kisunla in this lay summary for ease of reading.

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

What is Kisunla 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.

Kisunla contains the active substance donanemab, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Kisunla 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 doctor will perform testing to make sure that Kisunla is right for them.

How does Kisunla work?
Kisunla belongs to a group of medicines called amyloid-targeting antibodies. This medicine works by removing a sticky protein called beta-amyloid from the brain that is believed to cause Alzheimer's disease and its advancement.

How is Kisunla used?
The pharmaceutical form of this medicine is concentrate for solution for infusion (sterile concentrate) and the route of administration is intravenous infusion.

Kisunla will be given to the patient by a healthcare professional, through a drip in the vein of the patient's arm (intravenous infusion) over at least 30 minutes. After each infusion the patient will be monitored for allergic reactions for a minimum of 30 minutes.

The recommended dose of donanemab is 1400 mg. The patient will usually receive a dose of Kisunla once every 4 weeks. When starting the treatment with Kisunla, the patient will receive 700 mg once every 4 weeks for the first three doses.

The patient's doctor will decide how long they are treated with Kisunla. However, the total duration of treatment with Kisunla should not exceed 18 months.

For further information on how Kisunla 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 the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Kisunla have been shown in studies?
Kisunla was evaluated in a main study (Phase III Study TRAILBLAZER-ALZ 2) involving 1736 patients with early Alzheimer's disease that had mild cognitive impairment, mild dementia and evidence of amyloid pathology. The level of a protein call TAU, which is involved in Alzheimer's disease, in the brain was also measured.

The study looked at changes in patient's brain cognition and function, measured by clinical tools such as the integrated Alzheimer's Disease Rating Scale (iADRS). Other tools used by doctors to measure Alzheimer's disease were also used, such as CDR-SB, ADAS-Cog13, and ADCS-iADL.

In this study, the patients received either 700 mg Kisunla every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks (860 patients) or placebo (a dummy infusion, 876 patients) for up to 72 weeks.

At week 76 of the study, patients treated with Kisunla had statistically significantly less clinical progression in their Alzheimer's disease compared to patients that were treated with the placebo, with consistency across measures of cognition and function. This was assessed by change in iADRS score from baseline.

The ability to slow disease progression seems to be influenced by whether patients carry the ApoE4 gene. In this Phase 3 study, patients treated with Kisunla that were carriers and non-carriers were associated with less decline on their iADRS and CDR-SB scores and a significant reduction in amyloid plaque compared with placebo. Reduction of amyloid plaque and slowing of decline was smaller for patients with two copies of the gene.

What are the possible side effects of Kisunla?
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.

Kisunla can potentially cause serious side effects, such as swelling in areas of the brain with or without small spots of bleeding in or on the surface of the brain (Amyloid Related Imaging Abnormalities, ARIA).

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.

Why was Kisunla approved?
It was concluded that Kisunla has been shown to be effective in the treatment of early stages of Alzheimer's disease in adults who carry one copy the ApoE4 gene or in adults who do not carry it. 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.

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

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

The following safety concerns have been recognised for Kisunla:

Summary of safety concerns	
Important identified risks	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Hypersensitivity events (including IRR)
Important potential risks	Intracerebral haemorrhage > 1 cm[a]
Missing information	Accelerated brain volume loss Long-term safety

Abbreviations: ARIA-E = amyloid-related imaging abnormality–oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition; IRR = infusion-related reaction.

[a] Intracerebral haemorrhage >1 cm includes cerebral haemorrhage and haemorrhagic stroke.

The company responsible for Kisunla is required to perform further studies and to provide additional measure to minimise the risks with this medicine. The studies include the following:

- Mandatory PASS: Registry-based observational study to characterise safety of donanemab in UK patients
- registry-based sub-study: healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the UK
- secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients
- study AACI: assessment of safety, tolerability, and efficacy of donanemab in early symptomatic Alzheimer's disease (long-term extension phase; AACI-LTE)

Additional risk minimisation activities will be implemented for donanemab. These activities include the following:

- educational materials for prescribers and radiologists on important safety risks related to the use of donanemab such as ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracerebral haemorrhage >1 cm
- a patient card designed to enhance the awareness and knowledge of patients and caregivers about the safety concerns with donanemab as well as inform physicians of ARIA differential in an emergency setting.

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 Kisunla 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 are satisfactory.

Other information about Kisunla
A marketing authorisation application for Kisunla was received on 28 July 2023 and a marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 23 October 2024.

The full PAR for Kisunla follows this summary.

This summary was last updated in January 2025.

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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 Kisunla 350 mg concentrate for solution for infusion (PLGB 14895/0338) could be approved.

Donanemab is indicated for adult patients with Alzheimer's disease. Treatment with donanemab should be initiated in patients with evidence of amyloid beta pathology and either mild cognitive impairment or mild dementia.

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

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), a a full-dossier application.

The majority of non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). Other studies (8222743, MB135) were not intended to be GLP-compliant: one was a 6 month pharmacology study in PDAPP transgenic mice in which safety evaluations were also made and the second was also in transgenic mice and was an exploratory study into the risk of cerebral microhaemorrhages.

All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the granting of a class waiver MHRA-01-23-CW01. This waiver was granted as Alzheimer's disease does not occur in the paediatric population.

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 November 2023 and April 2024. At the 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 in August 2024. Following the provision of further data, the CHM advised the grant of a Marketing Authorisation.

A marketing authorisation application for Kisunla was received on 28 July 2023, and marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 23 October 2024.

II QUALITY ASPECTS

II.1 Introduction

This product contains 350 mg of donanemab in 20 ml of concentrate for solution for infusion (17.5 mg/ml). In addition to donanemab, this product also contains the excipients citric acid anhydrous, polysorbate 80, sodium citrate dihydrate, sucrose, and water for injection.

The finished product is packaged in a 20 ml single-dose clear type I glass vial, with a chlorobutyl elastomer stopper and an aluminium seal with a polypropylene cap in pack sizes of 1 vial.

II.2 ACTIVE SUBSTANCE

rINN: Donanemab

Chemical Name: Immunoglobulin G1, anti-(human pyroglutamyl Aβ (3-x) peptide) (human clone LY3002813 γ1-chain), disulfide with human clone LY3002813 κ-chain, dimer

Chemical Structure: Recombinant humanised immunoglobulin G1 (IgG1) isotype monoclonal antibody composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. Each heavy chain contains a single N-linked glycosylation site at Asn295. The N-linked glycosylation structure is predominantly a fucosylated, complex biantennary glycan without galactose residues on either arm (G0F).

Molecular Weight: 147,968 Da (G0F/G0F form)

Appearance: Clear to opalescent, colourless to yellow to brown solution

The amino acid sequence for donanemab is shown in the figures below. The sequence of the variable region is shown in bold font, and sequence of the constant region is shown in regular font. The complementarity determining regions (CDRs) are shown in bold font and underlined. The site of N-linked glycosylation at Asn295 is shown in bold font and double underlined.

Figure 1: Light chain amino acid sequence.

```
        10         20         30         40         50         60
DIVMTQTPLS LSVTPGQPAS ISCKSSQSLL YSRGKTYLNW LLQKPGQSPQ LLIYAVSKLD

        70         80         90        100        110        120
SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCVQGTHYP FTFGQGTKLE IKRTVAAPSV

       130        140        150        160        170        180
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL

       190        200        210       219
SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
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Figure 2: Heavy chain amino acid sequence.

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        10         20         30         40         50         60
QVQLVQSGAE VKKPGSSVKV SCKASGYDFT RYYINWVRQA PGQGLEWMGW INPGSGNTKY

        70         80         90        100        110        120
NEKFKGRVTI TADESTSTAY MELSSLRSED TAVYYCAREG ITVYWGQGTT VTVSSASTKG

       130        140        150        160        170        180
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL

       190        200        210        220        230        240
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCPPCPAP ELLGGPSVFL

       250        260        270        280        290        300
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV

       310        320        330        340        350        360
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ

       370        380        390        400        410        420
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV

       430        440  444
FSCSVMHEAL HNHYTQKSLS LSPG
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Donanemab is not the subject of a Ph.Eur. monograph.

Donanemab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

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 starting materials and reagents.

Control of potential adventitious agents in the manufacture of donanemab 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 retest period 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(s)

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, the following shelf life and storage conditions are acceptable and listed in the product information:

Unopened vial:
2 years

Store in a refrigerator (2 °C to 8 °C). Keep the vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Once removed from the refrigerator, the vial may be stored unrefrigerated for up to 3 days at room temperature 20°C to 25°C, prior to preparation of the diluted solution for infusion.

Diluted solution for infusion
Chemical and physical in-use stability has been demonstrated for up to 72 hours at 2°C to 8°C or for up to 12 hours at room temperature (20 to 25°C). From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

If dilution has taken place in controlled and validated aseptic conditions, the donanemab dosing solution may be stored for up to 72 hours at 2°C to 8°C or for up to 12 hours at room temperature 20°C to 25°C.

Storage times include the duration of infusion. Do not freeze the diluted solution.

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 was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

Production and deposition of amyloid beta protein in plaques in the brain likely contributes to development of Alzheimer's disease. Extracellular plaque deposition is thought to be a causative factor in the initiation of neurodegeneration; development of intracellular neurofibrillary tangles also likely contributes.

The company intended to identify and develop an antibody that would be selective and bind only to an antigen present in deposited plaque in brain tissue: this should then engage its target and facilitate microglial-mediated removal of plaque. In contrast to other antibodies that target soluble amyloid beta, this profile, by not binding to soluble amyloid beta monomers, donanemab would have greater activity against plaque which, the company anticipated, would lead to better clinical efficacy.

Donanemab is an antibody directed at insoluble Aβp3-42 (N3pG or N3pE). This peptide arises due to amino terminal proteases trimming the first two amino acids from the peptide followed by cyclisation of the functional group to form a pyrol ring at the amino terminus (pyro-glutamate). N3pG peptide accumulates early in the deposition cascade but is a minor component of plaque (~0.1-1% according to the company). By targeting this protein, the drug aids in clearance of amyloid plaques leading to benefit to the patient of either disease stabilisation or slowing of progression of decline in cognitive function. Donanemab acts by microglial-mediated phagocytosis.

PDAPP mice were used extensively in development of donanemab. These mice express high levels of human amyloid precursor protein (APP) and develop cerebral amyloidosis with many of the neuropathological hallmarks of the human disease. As they age, they show region-specific accumulation of amyloid beta in the hippocampus and cortex, similar to that in patients with Alzheimer's disease, with consistent presence of amyloid plaque from ~12 months of age, with, over time, development of substantive accrual of the pharmacological target, PyroGlu-3 amyloid beta within the plaque.

The pharmacokinetics (PK) and toxicokinetics (TK) of donanemab have been characterised in cynomolgus monkeys. Additionally, PK/TK of mE8c, the murine surrogate of donanemab were assessed in aged transgenic PDAPP mice and CD-1 mice.

Biochemical characterisation of brain lysates at 12 months of age demonstrates very low levels of PyroGlu-3 Amyloid beta, ~0.6% of the total deposited amyloid beta peptide. Although age of onset, brain cortical region affected and general abundance of PyroGlu-3 amyloid beta deposition varied among different disease-like transgenic mice, this same general paradigm was found i.e. that general amyloid beta deposition precedes and greatly exceeds deposition of pyroGlu-3 amyloid beta. Concentrations of the pyroGlu-3 amyloid beta peptide necessary to support target-mediated pharmacology is a feature limited to aged transgenic animals.

PDAPP mice are considered suitable for use in toxicological evaluations of donanemab, but as that is a humanised antibody, it was likely to elicit antibody if given to mice; therefore, in PDAPP mice, a testing programme based on use of murine antibodies was also applied.

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

Pharmacology

1. **Study BTDR128** - *In Vitro* Binding Affinity and Epitope Determination of N3pG Antibodies by Surface Plasmon Resonance
2. **Study NDG73** - *Ex Vivo* Phagocytosis Studies with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)
3. **Study NDG74** - *Ex Vivo* Target Engagement Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanised Antibodies (LY3002813)
4. **Study NDG75** - *In Vivo* Target Engagement Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanised Antibodies (LY3002813)
5. **Study NDG76** - *In Vivo* Plasma Aβ Accumulation Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanised Antibodies (LY3002813)
6. **Study NDG77** - *In Vivo* Therapeutic Plaque Lowering Studies in Aged PDAPP Mice with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)
7. **Study NDG78** - In Vivo Plaque Lowering Studies in Aged PDAPP Mice with Anti-N3pG Antibody mE8c (Murine Surrogate for LY3002813) to Determine Minimum Efficacious Dose
8. **Study NDG79** - *In Vivo* Plaque Prevention Study in PDAPP Mice with Anti-Aβ Antibodies Including mE8c (Murine Surrogate for LY3002813)
9. **Study NDG80** - *In Vivo* Microhaemorrhage Study in Aged PDAPP Mice with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)

Pharmacokinetics

10. **Study 8301447**- Serum Pharmacokinetics of LY3002813 in Cynomolgus Monkeys After Intravenous or Subcutaneous Administration: Comparison of 3 Material Lots
11. **Study 8237314**- Pharmacokinetics of LY3002813 in Cynomolgus Monkeys Following a Single Intravenous or Subcutaneous Dose of 1 mg/kg LY3002813
12. **Study 8253105** - Serum and Plasma Exposure with Three Lots of mE8c (LSN3026818) in CD1 Mice Following a Single Subcutaneous Dose of 10 mg/kg

Toxicology

13. **Study 8242713** -Repeat-Dose Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY3002813 by Intravenous Injection Once Weekly for 6 Weeks with a 3-Month Recovery Phase
14. **Study 8222-743** - Chronic Pharmacology/Toxicity Study in Aged Female PDAPP Mice Given Weekly Subcutaneous Doses of mE8 Derivative C (Murine Analog of LY3002813) for Six Months
15. **Study 504531** - Repeat-dose Toxicity and Exposure Study in PDAPP Mice Given LSN3026818, mE8 Derivative c (mE8c, Murine Analog of LY3002813) by Subcutaneous Injection Once Weekly for 6 Months
16. **Study 504299** - Repeat-dose toxicity and exposure study in PDAPP mice given LSN3026818, mE8 Derivative c (mE8c, murine analog of LY3002813) by subcutaneous injection once weekly for 6 weeks
17. **Study 20008867** - Tissue cross-reactivity of LY3002813 with human and cynomolgus monkey tissues *ex vivo*
18. **Study MB135** - Cerebral microhaemorrhage and neuropathology study in aged PDAPP mice given LSN3026818, mE8 Derivative C (mE8c, murine analog of LY3002813), by intraperitoneal injections weekly for 3 months

Compliance with Good Laboratory Practice (GLP) is expected for the tissue cross reactivity study (20008867) and general toxicity studies, which were done in monkeys (8242713) and in transgenic mice (eg 504299). These studies were done either in Canada or in the United States and compliance with GLP is accepted.

Other studies (8222743, MB135) were not intended to be in compliance GLP-compliant: one was a 6 month pharmacology study in PDAPP transgenic mice in which safety evaluations were also made and the second was also in transgenic mice and was an exploratory study into the risk of cerebral microhaemorrhages.

Please note that during its development, donanemab was known as LY3002813, LA443, N3pG Mab, B12L and anti-N3pG amyloid beta IgG1 monoclonal antibody and so this may be referenced.

III.2 Pharmacology

In vitro pharmacology

Mice were immunised with a modified form of amyloid beta (called N3pG) present only in plaque resulting in monoclonal antibodies that specifically bind amyloid plaque, but not soluble amyloid beta or its precursor APP (amyloid precursor protein). One was selected and termed mE8 (also LSN3026818) and from this by humanisation, donanemab (here called LY3002813 and also called B12L) was created. The murine antibody was made in both mouse IgG1 and IgG2A isotypes: the IgG1 isotype is called mE8 and the IgG2a isotype is called m8Ec.

Study BTDR128 - *In Vitro* Binding Affinity and Epitope Determination of N3pG Antibodies by Surface Plasmon Resonance

The aim of the work reported in study BTDR128 was to determine those residues of N3pG amyloid beta peptides that impact binding of donanemab (LY3002813, B12L) and to confirm that it had the same epitope specificity as its murine parental antibody, mE8c.

Affinity of antibodies for modified amyloid beta was characterised by surface plasmon resonance (Biacore): this monitors formation and dissociation of biomolecular complexes on a sensor surface by measuring changes in reflected light as the interaction occurs. Changes in incident light over time are proportional to the mass concentration of the interacting biomolecules on the biosensor surface.

Donanemab antibody capture was achieved by covalently immobilising recombinant protein A to flow cells of a sensor chip by amine coupling. For the mouse IgG2A molecule m8Ec (here called LSN3026818), antibody capture was achieved by covalently immobilising goat anti-mouse IgG to flow cells of a sensor chip. Association and dissociation rates were evaluated and binding parameters determined.

The specific epitope to which binding took place was also explored. For this a series of amyloid beta peptides with positional changes (glycine mutants) were synthesised to assess the impact of a given residue on antibody binding and thereby identify characteristics and sequence required for antibody recognition. The company used Biacore methods to test binding of donanemab and mE8c to each of a set of derivatives of pE3-16 peptide, the N-terminal 14 residues of N3pG amyloid beta.

Table 1: Test Articles.

Test Articles

Test Article	[redacted]	Stock Concentration	Source (produced at Lilly unless noted otherwise)
LY3002813 (human IgG1)		4.2mg/mL	Recombinant expression & purification from CHO cells
LSN3026818 (mouse IgG2A)		9.25mg/mL	Recombinant expression & purification from CHO cells
Abeta N3pE-42 peptide		1.0 mg/mL H2O	Anaspec
Abeta E3-16-biotin		5mg/mL PBS	Abgent EFRHDSGYEVHHQK-biotin
Abeta pE3-16-biotin			Abgent Pyr-EFRHDSGYEVHHQK-biotin
Abeta pE3-G4-16-biotin			Abgent Pyr-EGRHDSGYEVHHQK-biotin
rodent Abeta mpE3-16-biotin			Abgent Pyr-EFGHDSGFEVHHQK-biotin
Abeta pE3-G6-16-biotin			Abgent Pyr-EFRGDSGYEVHHQK-biotin
Abeta pE3-G7-16-biotin			Abgent Pyr-EFRHGSGYEVHHQK-biotin
Abeta pE3-G8-16-biotin			Abgent Pyr-EFRHDGGYEVHHQK-biotin
Abeta pE3-F10-16-biotin			Abgent Pyr-EFRHDGGFEVHHQK-biotin

Results: The two antibodies, donanemab and mE8c had the same epitope specificity: they do not recognise rodent pyroglutamate amyloid beta (mouse pE3-16) and have over 100-fold weaker affinity to the amyloid beta peptide beginning with glutamate (E3-16) in place of pyro-glutamate.

The relative importance of the epitope residues and their impact on affinity are: F4 ~ R5 > pE3 > D7 >H6 >> Y10. Neither antibody bound to human Aβ 1-40 peptide at concentrations up to 1 μM. Affinity constants (KD) for donanemab (LY3000283) and for mE8c were 0.82 and <0.2 nM respectively.

The company concluded that these antibodies bind to N3pG but do not recognise the natural N terminus of amyloid beta peptide – they require a modified pyro-Glu N-terminus (amino acid 2) for high affinity binding. The epitope extends to amino acid 7 of human amyloid beta peptide.

Study NDG73 - *Ex Vivo* Phagocytosis Studies with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)

The mode of action of donanemab relies on opsonisation of deposited target and its subsequent removal by activated microglia. In report ndg73, the company described experiments into this mode of action by phagocytosis: the aim was to determine if the antibodies facilitated microglial phagocytosis of plaque sourced from the brain of a patient with Alzheimer's disease.

The company had devised anti-N3pG antibodies either for minimum (IgG1, mE8) or maximum (IgG2a, mE8c) effector functions using murine glial cells (note: the IgG1 format in mice is less active than IgG2a). The study addressed whether antiN3pG antibodies bind to deposited plaque and can cause their clearance via a phagocytotic mechanism of action.

The company used a control IgG2a antibody and the following antibodies:

- 3D6 – this targets amyloid beta 1-x
- 21F12 – this is a murine IgG1 antibody that targets amyloid beta x-42
- 2G3 – this is a murine IgG1 antibody that targets amyloid beta x-40
- mE8 and mE8c – both target amyloid beta p3-x (murine surrogates of donanemab).

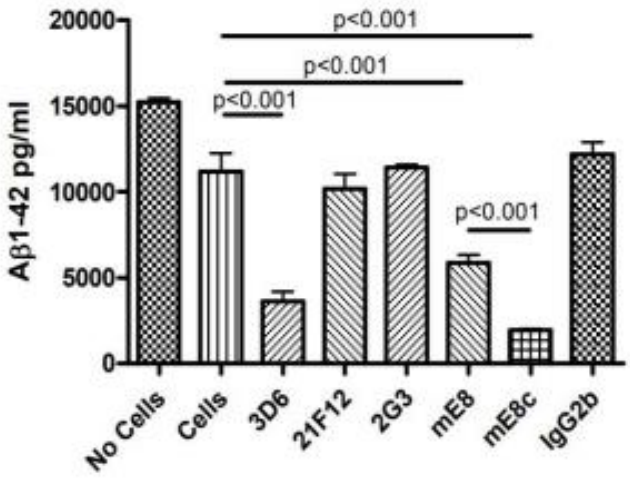
The murine antibodies 21F12 and 2G3 bind deposited amyloid beta quite poorly but bind soluble amyloid beta.

To assess phagocytosis activity, the company sourced brain tissue from a patient with Alzheimer's disease and embedded this in matrix, sectioned it to 20 microns and mounted it: it was then placed in 24-well tissue culture plates. 64 consecutive sections were incubated with or without test antibodies (10 microg/ml). Primary murine microglia (8 x 10(5) cells) were then added to sections and incubated for 24 hours when media were removed and tissue sections and cells were further prepared by homogenisation and amyloid beta 1-42 was quantified by ELISA. Analysis of remaining amyloid beta 1-42 present in the tissue section is a means to demonstrated that antibodies facilitated clearance of deposited plaque.

Results: As shown in Figure 3 below, addition of microglial cells lead to a reduction in amyloid beta 1- 42 which was enhanced by addition of the antibody 3D6. This is interpreted as the antibody acting to stimulate phagocytosis of bound amyloid by the murine glial cells. The company noted that the amino-terminal antibodies significantly facilitated the clearance of deposited plaque ($p < 0.001$).

mE8c, the N3pG antibody with maximal effector function (IgG2a) cleared more plaque than did mE8, the N3pG antibody with minimal effector function (mE8, IgG1). Control antibodies (21F12, 2G3), which lack the ability to bind the target, did not alter the amount of amyloid beta cleared by the microglia cells alone.

Figure 3: *Ex vivo* antibody facilitated phagocytosis of deposited Aβ from Alzheimer's disease brain sections.



Frozen AD brain sections (20 µm) were incubated with 10 µg/mL of each antibody for 1 hour at 37ºC in 24-well plates (4 wells per treatment). At the conclusion of the incubation, primary murine microglia (C57/BL6) were placed on top of each section ($8x10^{5}$ cells), and the incubation continued for an additional 24 hours. After the incubation, the cells and tissue section were homogenized in 5.2M guanidine buffer and the $A\beta_{42}$ was determined by ELISA. Each bar represents the mean +/- SEM, N = 4 wells for each treatment except the no cells control (N = 35).

The company concluded that these results show that exogenous addition of the amino terminal antibodies 3D6, mE8, or mE8c all facilitated the targeting of the microglia to the Alzheimer's plaque.

Study NDG74 - *Ex Vivo* Target Engagement Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanised Antibodies (LY3002813)

In study ndg74, the company reported on the ability of several anti-N3pG antibodies to bind ex vivo to deposited amyloid beta in brain sections from aged PDAPP mice and from Alzheimer's disease patients. Testing determined whether the murine surrogate anti-N3pG antibody (mE8) or humanised antiN3pG antibodies (R17, R17L, B12L, and hE8L) would bind to plaque deposits in these tissues. 3D6 (anti-Aβ1- x) was also used in this testing.

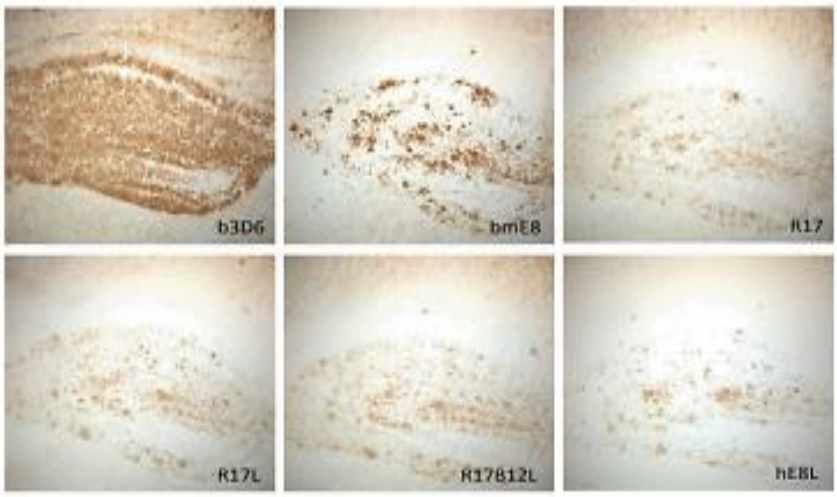
These antibodies were:

- R17 (anti-Aβp3-x)
- R17L (anti-Aβp3-x))
- R17B12L (anti-Aβp3-x
- hE8L (anti-Aβp3-x), and
- control human IgG.

For this, biotinylated derivatives of each test antibody were created. Cryostat serial coronal sections (10 microm thick) were created from a 24-month old PDAPP mouse. The same (20 microm thick) were also created from the brain of an Alzheimer's patient. Each were incubated with biotinylated test antibodies (at 3 or 10 microg/ml for mouse or human brain respectively) and secondary horseradish peroxidase-conjugated derivatives specific for biotin or human IgG used to visualise deposited plaque.

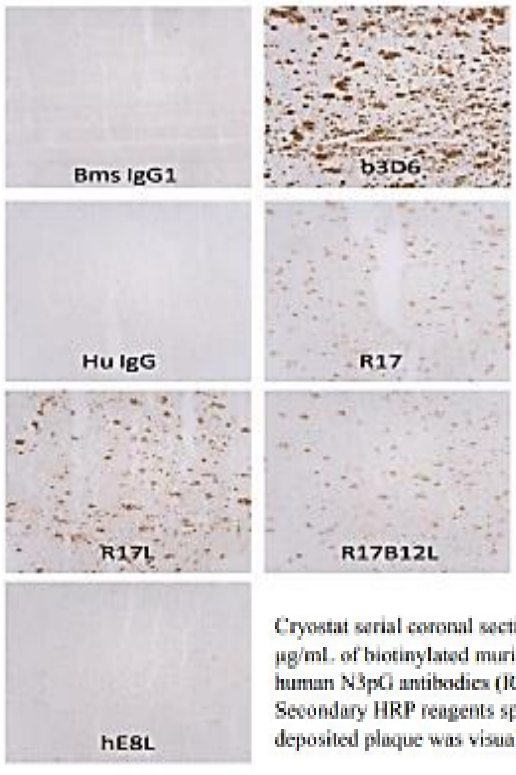
Results: Biotinylated 3D6 antibody (antiAβ1-x) labelled deposited amyloid beta in the PDAPP hippocampus. Biotinylated mE8 (anti-Aβp3-x) labelled only a subset of deposits and similar plaque labelling for all human non-biotinylated N3pG antibodies (compared to the mE8) was seen. In examining binding to deposited amyloid beta in brain tissue from a patient with Alzheimer's disease, 3D6 (positive control) intensely labelled many amyloid beta plaques. Several of the human antibodies to N3pG bound similarly to deposited amyloid beta.

Figure 4: Ex vivo histological analysis of deposited Aβ in aged PDAPP brain.



Cryostat serial coronal sections (10μm thick) from a 24-month old PDAPP mouse were incubated with 10 μg/mL of biotinylated murine antibodies (3D6, anti-$A\beta_{1-x}$; mE8, anti-$A\beta_{p3-x}$) or human N3pG antibodies (R17, R17L, R17B12L, or hE8L). Secondary HRP reagents specific for biotin or human IgG were employed and the deposited plaque was visualized with DAB-Plus (DAKO). Brain sections incubated with control biotinylated murine IgG or control human IgG were devoid of staining.

Figure 5: Ex vivo histological analyses of deposited Aβ in Alzheimer's disease brain.



Cryostat serial coronal sections (20μm thick) from an AD brain were incubated with 3 μg/mL of biotinylated murine antibodies (3D6, anti- Aβ1-x; control murine IgG) or human N3pG antibodies (R17, R17L, R17B12L, hE8L, or control human IgG). Secondary HRP reagents specific for biotin or human IgG were employed and the deposited plaque was visualized with DAB-Plus (DAKO).

The company concluded that the mE8 bound to the deposited plaque in this ex vivo testing. Several of the humanised anti-N3pG antibodies did so too. The humanised anti-N3pG antibodies R17L, R17, and R17B12L engage the deposited target when added exogenously to brain sections from aged PDAPP mice or Alzheimer's disease patients. For this assessment, it is key to understand that the mE8 construct bound to murine amyloid beta

In vivo **pharmacology**

Study NDG75 - *In Vivo* Target Engagement Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanized Antibodies (LY3002813)

In study ndg75, in vivo engagement of several antibodies to amyloid beta structures was investigated. This study was done in PDAPP mice, aged 16-19 months old who were dosed with biotinylated test antibody intraperitoneally. The main aim was to determine if these crossed the blood brain barrier and engage with the target in the brains of these mice. In particular, binding to deposited plaque was the object of evaluation.

In brief, mice were dosed with each biotinylated antibody detailed as follows:

Murine antibodies

- 3D6 (anti-Aβ1-x)
- mE8 (anti-Aβp3-x)
- control murine antibody (IgG1).

Humanised antibodies

- R17 (anti-Aβp3-x)
- R17L (anti-Aβp3-x)
- R17B12L (anti-Aβp3-x)
- hE8L (antiAβp3-x)
- control human IgG.

Mice were dosed with murine antibodies at 4 or 40 mg/kg once weekly on 4 occasions and were killed 3 days after their last dose. Further mice were dosed once only with the humanised antibodies at 10 or 40 mg/kg, except for R17 which was dosed at 20 and 80 mg/kg; mice were killed 3-days later.

The use of a single dose of the humanised antibodies was intended to reduce the risk that immune system reactions in mice might compromise the aims of the study. The design was also intended to allow the antibodies time to equilibrate within the brain.

From all mice, one hemi-brain was flash frozen for histological analyses. The amount of in vivo target engagement was determined by histological examination. For this, cryostat serial coronal sections (12 microm thick for the sub-chronic study or 20 microm thick for the acute study) were prepared. For the sub-chronic study, slides were stained to allow visualisation of murine biotinylated antibody and staining patterns captured as images under a microscope by digital camera. For the acute study, slides were stained with a donkey anti-human antibody and the human antibody was visualised as with the murine antibodies.

In order to determine the total amount of deposited amyloid beta in these brains, parallel slides were prepared and stained with biotinylated 3D6 and detected and the two sets of slides were compared to allow quantification of stained areas to determine the net area

stained in the hippocampus. The net target engagement was calculated for each mouse by dividing % area of hippocampus positive for the endogenous human antibody by % area of the hippocampus positive for total deposited plaque (as determined by the exogenous addition of biotinylated 3D6).

In addition, in plasma taken at the conclusion of the acute study, concentrations of the humanised antibodies were determined by antigen capture ELISAs. The net target engagement calculated above was then divided by the plasma exposure and the resulting PK-normalised target engagement was multiplied by 1000 (in order to have whole numbers).

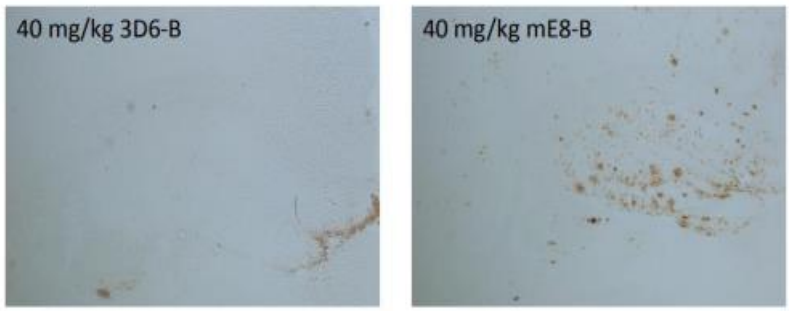
Results: Antibody to the amino terminal of amyloid beta (3D6) showed a lack of target engagement with limited target engagement localised along the hippocampal fissure. The company interpreted this as the antibody has bound to soluble target and so cannot efficiently bind to the deposited Aβ.

By contrast, antibody that targets N3pG regions (mE8) engaged with deposited target throughout the hippocampus and cortical regions, considered as critical brain regions for it to have its therapeutic effect. Figure 6A shows the binding of each of 3D6 and mE8 in this testing with the latter being clearly more extensive. The same pattern was shared with the human anti-N3pG antibodies (i.e. hippocampal and cortical engagement).

Analysis of the level of target engagement in the hippocampus demonstrated that R17, R17L, and R17B12L trended to have better engagement than hE8L. In terms of % target engaged, normalised values are in Figure 6B.

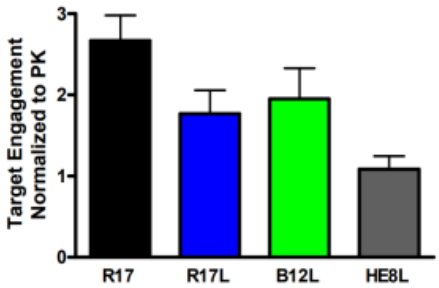
Figure 6: Aβ antibody in vivo target engagement studies in aged PDAPP mice.

A.



Images demonstrate that 3D6 only engages deposited plaque along the hippocampal fissure whereas the N3pG antibody mE8 engages deposited plaque throughout the hippocampal and cortical regions.

B.



The final number of mice analyzed for each antibody was: R17, N = 7; R17L, N = 9; B12L, N = 10; hE8L, N = 10. Error bars represent the standard error or the mean (SEM).

The company concluded that humanised anti-N3pG antibodies R17L, R17, and R17B12L engage the deposited target when administered peripherally to aged PDAPP mice: this shows they cross the blood brain barrier. Importantly, antibody that binds both soluble and insoluble amyloid beta bound to the soluble form so extensively that it did not engage the intended deposited target.

Study NDG76 - *In Vivo* Plasma Aβ Accumulation Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanised Antibodies (LY3002813)

The epitope targeted by donanemab is termed N3pG and is selectively found in deposited plaque: it is present in the brains of both aged PDAPP mice and in patients with Alzheimer's disease. The company suggested that selective binding to deposited forms of amyloid beta present only in plaque will yield better target engagement since the antibody will not bind soluble amyloid beta. In essence this will direct the effect of the drug to the deposited plaque without directly affecting soluble amyloid beta.

The company tested whether its antibodies could bind soluble amyloid beta in an in vivo study in which PDAPP mice were dosed once, subcutaneously with test antibody and then plasma amyloid beta concentrations were measured 24 hours later. Increases in plasma amyloid beta 1-40 will indicate antibody binding to physiological levels of endogenous Aβ1-40.

The antibodies used were:

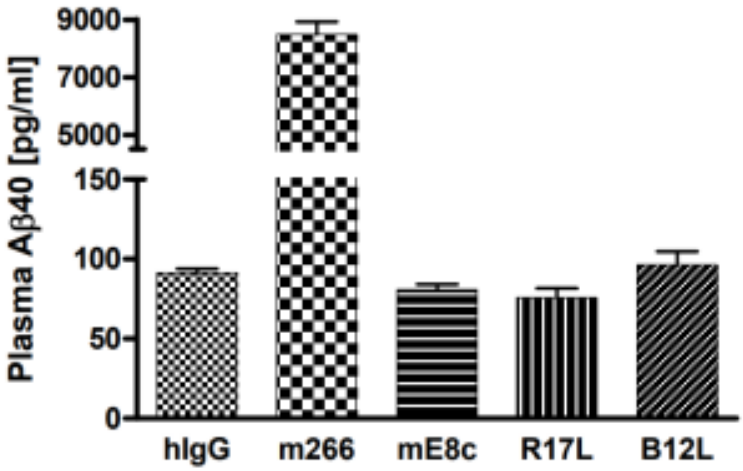
- mE8c (anti-Aβp3-x
- R17L (anti-Aβp3-x)
- R17B12L (anti-Aβp3-x)
- control human IgG.

As a positive control further mice were given an antibody which is known to bind soluble amyloid beta, m266 (anti-Aβ16-24; lot A4081269).

Mice used in this study were aged 5-7 months old. They were injected with each antibody at a dose of 10 mg/kg and 24 hours later, plasma was obtained and amyloid beta 1-40 was measured by sandwich ELISA.

Results: Plasma concentrations of amyloid beta 1-40 are shown in Figure 7 below. Whereas mice given the positive control antibody, m266, had ~100-fold increase at 24-hours after dosing, in mice given each of the other antibodies to N3pG, there was no change in plasma amyloid beta 1-40.

Figure 7: In vivo plasma $A\beta_{40}$ accumulation in young PDAPP mice dosed with anti-Aβ antibodies.



PDAPP mice (N = 4 per antibody) were dosed subcutaneously with 10 mg/kg of mE8c (murine anti-N3pG), R17L (humanized anti-N3pG), R17B12L (humanized anti-N3pG), m266 (murine anti-Aβ), and control human IgG antibodies. After 24-hours, plasma was isolated and the plasma $A\beta_{40}$ concentrations were determined by ELISA. The m266 antibody, which binds robustly to soluble Aβ, resulted in a ~100-fold elevation of plasma $A\beta_{40}$ ($p < 0.001$ compared to all other dose groups, Tukey's post-hoc from one way ANOVA), whereas the N3pG antibody treatment did not significantly increase plasma $A\beta_{40}$. The error bars represent the standard error or the mean (SEM).

The company concluded that these data support its claim that antibodies targeting N3pG do not bind to full-length amyloid beta in vivo.

Study NDG77 - *In Vivo* Therapeutic Plaque Lowering Studies in Aged PDAPP Mice with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)

In accordance with the concept that reducing plaque will address some of the features of Alzheimer's disease and noting that plaque is deposited long before clinical changes in patients are noted, the aim of treatment is to reduce plaque; this was tested in study ndg77 in aged PDAPP mice. However, the nature of the deposition differs between mice and patients in that the latter show steady but small plaque accrual (~3% increase in signal per year) whereas PDAPP mice have two main phases of deposition: log (middle aged; 6 to 18 months of age) and plateau (aged mice; 19 to 26 months of age).

During the log phase, amyloid beta deposits accumulate quickly with deposition being approximately 5-fold higher in the hippocampus compared to the cortex and mice show robust deposition even during the plateau phase where amyloid beta can increase by >30% in 3 months. The company noted that this poses a very high hurdle for studies in PDAPP mice to show reduction in plaque.

In this study, the company tested both mE8c which retains Fc effector function and mE8 which has minimal effector function and did so because the mode of action of donanemab is proposed to Fc-dependent phagocytosis. The only mechanism of action through which the N3pG antibodies could lead to plaque lowering is phagocytosis of existing plaque material. 3D6 was also tested.

The antibodies used in this experiment were:

- 3D6 (anti-Aβ1-x)
- mE8c (anti-Aβp3-x)
- mE8 (anti-Aβp3-x)
- control murine IgG2a.

PDAPP mice aged 23-24 months at the start of the study were used. They were dosed once weekly by intraperitoneal injection at a dose of 12.5 mg/kg for 3 months and then killed for analyses of hippocampal and cortical plaque content in one hemisphere. A further group of 15 mice, of mean age 24.5 months, were killed prior to any treatment and their amyloid content analysed.

The hippocampal and cortical tissues were homogenised and after further preparation steps, they were analysed by acid urea gel technology using Western blotting. Plasma samples were also obtained at necropsy and analysed by ELISA.

Results: Figures 8 and 9 show the amount of amyloid beta measured in the hippocampal and cortical tissues. In both cases, this increased in control mice after 3 months: the company indicated that as this was not statistically significant, this confirmed that mice were at the plaque plateau. 3D6 had no effect on to lower plaque. mE8 or mE8c each resulted in plaque lowering compared to controls: mE8 and mE8c lowered amyloid beta 42 by ~38 and ~53%, respectively indicating that the format of antibody with effector function trended to being more efficacious than the minimal effector function antibody; however, this difference did not reach statistical significance. Also, mice given mE8c antibody had ~30% lowering of amyloid beta 42 in the hippocampus as compared to the time zero mice suggesting clearance of previously deposited plaque. In cortical tissues, the results were similar but only mE8c significantly decreased amyloid beta 42 deposition.

Figure 8: Analysis of hippocampal plaque lowering studies in aged PDAPP mice treated therapeutically with anti-Aβ antibodies.

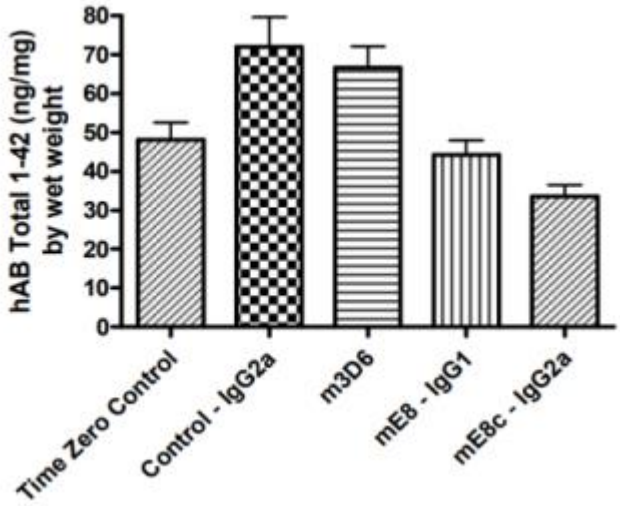
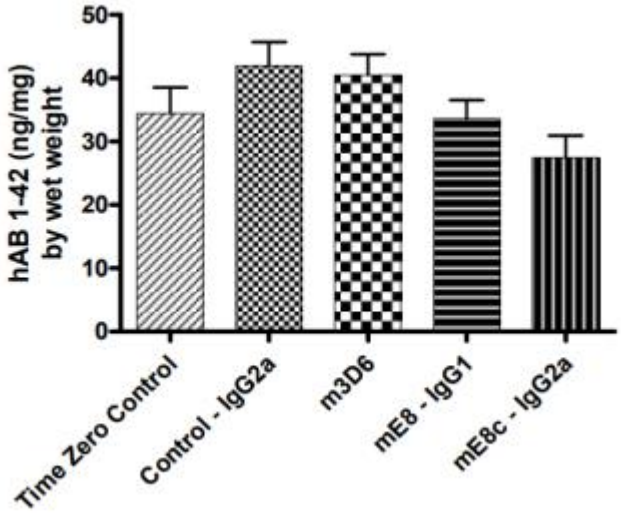


Figure 9: Analysis of cortical plaque lowering studies in aged PDAPP mice treated therapeutically with anti-Aβ antibodies.



Plasma IgG concentrations showed similar mean values for 3D6, mE8 and mE8c (not shown here). The company concluded that when used in aged PDAPP mice for 3 months each of mE8c and mE8 resulted in lower plaque concentrations. As there was a greater reduction in mice given mE8c, this was considered to be effector-function dependent. Also, mice given mE8c had lower plaque than mice at the beginning of the study.

Study NDG78 - In Vivo Plaque Lowering Studies in Aged PDAPP Mice with Anti-N3pG Antibody mE8c (Murine Surrogate for LY3002813) to Determine Minimum Efficacious Dose

Study NDG77 (described above) used only one dose level of antibody, 12.5 mg/kg. The company did a further study (NDG78) of similar design in PDAPP mice in which different dose levels of mE8c were given.

In this study, PDAPP mice, aged 16 months at study start, were dosed weekly with mE8c at doses of 0, 1.5, 4 or 12.5 mg/kg for 6-months. There were 30 mice in each group and they were dosed subcutaneously. The control group were given a murine IgG2a. At the end of dosing, plasma was obtained to quantify mE8c by ELISA and brains were processed for analysis of plaque amyloid beta content as described for the study above. As in the above study, there were a group of mice whose brains were analysed at time 0, at a mean age of 16 months, to determine the plaque load at this age.

Results: The concentration of mE8c in plasma at necropsy is in Figure 10. In this study, there was significant additional deposition over 6 months: deposited amyloid beta nearly doubled in hippocampus (Figure 11) and tripled in cortex (Figure 12). A dose-dependent decrease in amyloid beta 42 was seen in mice given mE8c in both hippocampus and in cortex. In hippocampus, 1.5, 4 and 12.5 mg/kg lowered deposited amyloid beta 42 by 15, 31 and 39% respectively; the reduction with the lowest dose was not statistically significant. Results in the cortex were similar except the reduction at 4 mg/kg was not significant.

Figure 10: Analysis of plasma mE8c IgG levels in aged PADAPP mice treated with varying doses of mE8c (anti-$A\beta_{p3-X}$, IgG2a).

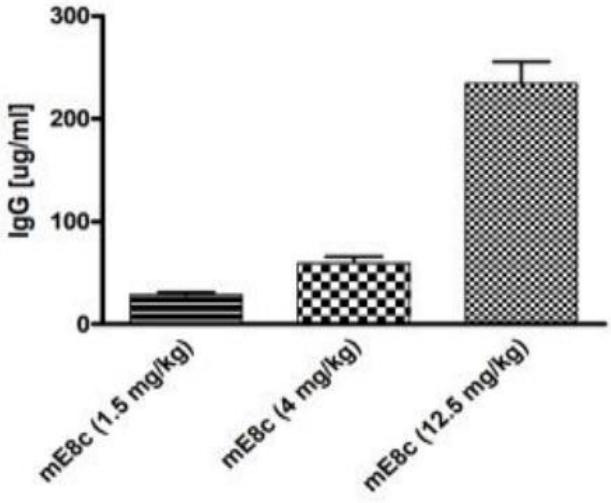


Figure 11: Analysis of hippocampal plaque-lowering studies in aged PDAPP mice treated with varying doses of mE8c (anti-$A\beta_{p3-X}$, IgG2a).

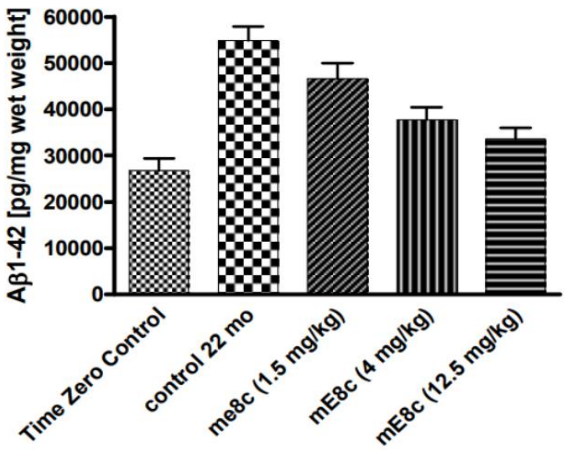
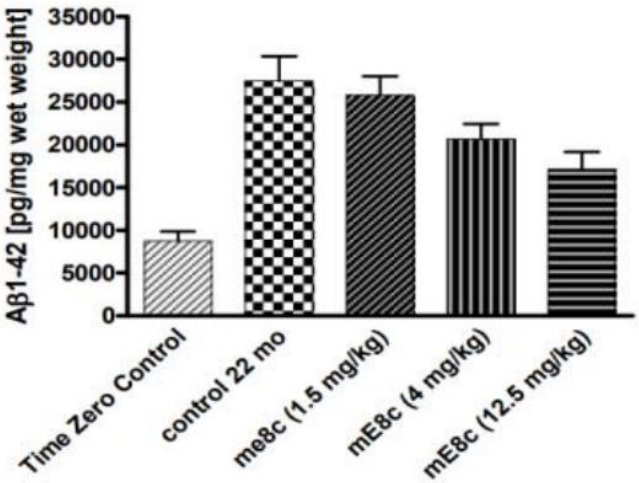


Figure 12: Analysis of cortical plaque-lowering studies in aged PDAPP mice treated with varying doses of mE8c (anti-$A\beta_{p3-X}$, IgG2a).



The company concluded that treatment led to significantly lower plaque in a dose-dependent fashion.

Study NDG79 - *In Vivo* Plaque Prevention Study in PDAPP Mice with Anti-Aβ Antibodies Including mE8c (Murine Surrogate for LY3002813)

The above studies used mice in which plaque was already established. Study NDG79 was done in younger mice, aged 5.5 months at the start of dosing, and was intended to evaluate the effect of mE8c to prevent plaque deposition in younger PDAPP mice, if dosed during the initial log phase of amyloid beta deposition.

A notable difference between PDAPP mice and human Alzheimer's patients is the amount of amyloid beta deposited per unit time. At first diagnosis, most patients are close to an apparent plaque ceiling and further plaque accrual is minimal (~3% increase in signal per year). PDAPP mice have two main phases of deposition: log (middle aged; 6 to 18 months of age) and plateau (aged mice; 19 to 26 months of age). During the log phase, Aβ deposits accumulate quickly with deposition being approximately 5-fold higher in the hippocampus compared to the cortex.

In this study, mice were dosed for 7 months from the age of 5.5 months. The test antibodies were:

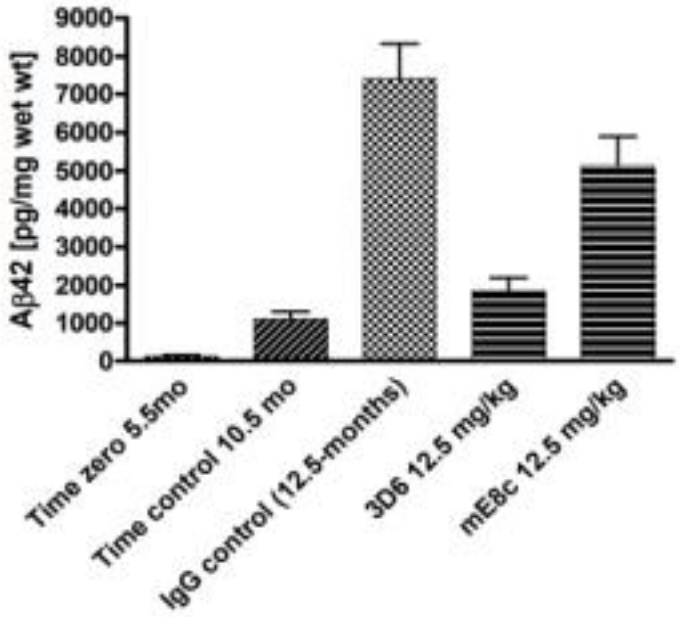
- mE8c (anti-Aβp3-x)
- 3D6 (anti-Aβ1-x)
- control murine IgG2a).

There were 30 mice in each group. They were dosed once weekly subcutaneously until the age of 12.5 months 12.5 mg/kg of 3D6, mE8c or control murine IgG2a. 30 mice were analysed for hippocampal amyloid beta content at the age of ~6 months of age: 30 further mice were analysed for hippocampal content of amyloid beta at age 10.5 months to follow deposition of amyloid beta 1-42. At the conclusion of dosing, brains were processed to allow quantification of amyloid beta 1-42 in hippocampus as in the previously described studies.

Results: Figure 13 shows the results from this study. Mice killed without treatment in this study at age 5.5 months lacked deposited amyloid beta 42. In mice killed at 10.5 months of age, hippocampal amyloid beta 42 increased 9-fold during the first 5 months and an additional 5-fold during the latter 2 months, to give ~45-fold increase over 7 months.

Use of 3D6 resulted in ~68% decrease of hippocampal amyloid beta 42 compared to the control but concentrations were still higher than in controls aged 10.5 months. Use of mE8c resulted in ~30% decrease in hippocampal amyloid beta 42 compared to controls, a non-significant reduction; mE8c did not prevent amyloid beta 42 deposition in younger PDAPP transgenic mice.

Figure 13: analysis of hippocampal plaque lowering studies in young PDAPP mice treated preventatively with anti-Aβ antibodies.



The company concluded that mE8c did not prevent Aβ42 deposition in young PDAPP transgenic mice.

Study NDG80 - *In Vivo* Microhaemorrhage Study in Aged PDAPP Mice with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)

Published studies showed that aged APP mice given certain antibodies to amyloid beta amino-terminal and carboxyl-terminal antibodies developed increased CAA-related microhaemorrhage (Pfeifer et al. 2002; Wilcock et al. 2004; Racke et al. 2005). The mechanism is not known: however, the company considered that antibody binding to deposited amyloid beta around blood vessels may be important.

The company established that Aβp3-x is a constituent of CAA in both patients with Alzheimer's disease and aged PDAPP mice. Study ndg80 sought to evaluate the occurrence of microhaemorrhages in aged PDAPP mice dosed with murine surrogate antibodies that had been shown in separate studies to decrease amyloid deposition. The study also investigated the role of effector function on microhaemorrhage risk by use of mE8 and mE8c.

The following antibodies were tested:

- 3D6 (anti-Aβ1-x; included as positive control for microhaemorrhage analyses)
- mE8c (anti-Aβp3-x; IgG2a)
- mE8 (anti-Aβp3-x; IgG1)
- control murine IgG2a.

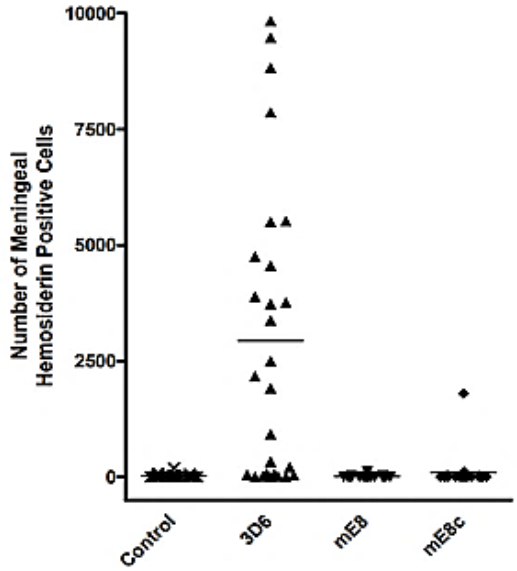
38-42 PDAPP mice aged 23 to 24-months were allocated to treatment with one of these antibodies and were dosed intraperitoneally once weekly at 12.5 mg/kg for three months. At the conclusion of dosing, mice were killed and plasma obtained to measure antibody: brains were also collected and one hemisphere was fixed in paraformaldehyde and used for histochemical analyses. A further group of 15 mice were killed at the start of dosing at age 24.5 months and brains similarly prepared for analyses.

Brain tissue was processed into three coronal sections each 2 to 3 mm in dimension; the centre section was processed into a paraffin block. Blocks were sectioned sequentially onto 50 slides. Each slide contained 4 sections; each section was 10 microns thick. Visualisation of microhaemorrhage used Perl's stain for ferric iron; sections were counter stained in Nuclear Fast Red (Vector) for contrast. 11 slides, ~160 microns apart, were stained per subject. Events were identified by a primary observer and confirmed by a secondary reviewer. A positive stain was denoted by: 1) bright or dark blue or a green-blue colour 2) a defined border within a cell or vacuole 3) staining residing within the tissue layer 4) no co-localised artifact. An event was determined by a discrete clustering around a centralised location, usually a blood vessel.

Results: The results are shown in Figure 14. 3D6 (anti-Aβ1-x, IgG2b) resulted in increases in CAA-related microhaemorrhage as had been expected based on prior studies (Racke et al. 2005). This occurred even in the absence of significant plaque lowering (see studies described above in which 3D6 did not reduce plaque).

Except for one mouse in the group given mE8c, use of each of mE8 and mE8c did not exacerbate microhaemorrhages, though they had lowered deposited amyloid beta in such mice (see studies described above in which they did reduce plaque). The company concluded that antibodies targeted at N3pG do not exacerbate CAA-related microhaemorrhage in aged PDAPP mice.

Figure 14: Prevalence of CAA-associated microhaemorrhage in aged PDAPP mice chronically treated with Aβ antibodies.



No studies on secondary pharmacodynamics, separate safety pharmacology studies or pharmacodynamic drug-drug interaction studies were conducted.

Behavioural pharmacology

In this application, the company did not present *in vivo* testing to show that mE8c could improve memory in mice or other information from studies that supported that donanemab could improve memory-functional deficits, where that deficit is due to established plaque.

The company noted that during the nonclinical development of donanemab, data from several of leading immunotherapy programmes demonstrated that beneficial behavioural effects observed in APP transgenic mice failed to translate into clinical benefit in human studies. From available literature, the bapineuzumab, solanezumab, and ponezumab nonclinical programmes demonstrated significant amelioration of behavioural impairments in APP transgenic mice when dosed with their corresponding surrogate antibodies, yet each programme failed to demonstrate significant decrease in cognitive decline in late-stage clinical.

The precise reason for the discordant behavioural translation is unknown; however, a likely contributor is the incomplete nature of the APP transgenic mouse models. APP transgenic mice are a robust model of Aβ deposition but do not develop many key features of AD (no tau paired-helical filaments or widespread neurodegeneration).

Importantly, many behavioural phenotypes observed in APP transgenic mice are present prior to the extracellular deposition of Aβ, suggesting over-expression of the APP transgene and/or neurodevelopmental alterations are influencing behavioural outcomes.

The PDAPP mouse model used in the non-clinical studies over expresses a human mutated APPV717F cDNA-based minigene driven by the platelet-derived growth factor promoter. These mice have elevated cortical synaptophysin immunoreactivity, cerebral hypometabolism, altered hippocampal synaptic transmission, and multiple neuroanatomical abnormalities (including hippocampal atrophy) at young ages prior to plaque deposition. However, the relevance of these changes to the pathogenesis of Alzheimer's disease is unclear and appears limited given the lack of prominent tau pathology or neurodegeneration in the mice.

Moreover, behavioural studies have suggested that PDAPP mice have age-independent and age-dependent learning or memory impairments. Nonclinical studies with the murine surrogate antibody for solanezumab (m266) demonstrated significant reversal of memory deficits in aged PDAPP mice without altering deposited Aβ levels, thereby, suggesting memory improvement was due to a mechanism of action independent from plaque removal.

Thus, due to the myriad of issues with behavioural assessments in PDAPP mice and the lack of clinical translation for several amyloid-targeting immunotherapy programmes that used other APP transgenic mice, the nonclinical development of donanemab focused on microglial-mediated plaque removal, a pharmacology endpoint that has shown robust translation in human patients in subsequent clinical trials.

The MHRA accepted the company's justification that the removal of amyloid beta from the central nervous system does not result in better performance by treated animals in such testing and that the converse has been shown, that there has been improvement in performance in animals given murine surrogate of solanezumab despite not altering deposited amyloid beta.

The MHRA noted that reducing amyloid might not be expected to resolve all issues in relation to impeded memory function.

Conclusions on pharmacology

Alzheimer's disease is associated with deposition of amyloid beta forming plaques in the brains of patients: by the time a patient is diagnosed, plaques are well established.

Donanemab (LY3002813) is a humanised IgG1 antibody directed at a region on amyloid beta protein, N terminal pyroglutamate (known as N3pE, N3pGlu or N3pG and also known as amyloid beta p3-x), present only in established plaques – it does not bind to or engage with soluble forms of amyloid. N3pG arises from proteases trimming 2 amino acids from the amyloid beta peptide, followed by cyclisation of the functional group to form a pyrole ring at the amino terminus (forming a pyro-glutamate).

It acts by binding to deposited amyloid plaque and, through its Fc region, activating microglial-dependent phagocytosis of deposited amyloid plaque. Removal of plaque aims to alter disease progression, slowing the decline in cognitive function that occurs in patients.

The company considered that antibodies that target both forms of amyloid beta, that is soluble and insoluble forms, will not be efficacious because they do not remove established plaques and this is, at least in part, because such antibodies bind to soluble amyloid beta to an extent where they have minimal binding to established plaque.

Use of donanemab, a humanised antibody, in mice would likely result in neutralising antibody responses and therefore for in vivo testing the company used murine versions of donanemab from which donanemab had initially been created by humanisation, termed mE8 and mE8c. To mimic donanemab's Fc activity, an IgG2a format was created (mE8c) and for studies to test the role of Fc effector effects, mE8 was also used which, as an IgG1 murine antibody lacks Fc effects. Donanemab and mE8c were shown to bind to amyloid beta p3-X peptide with high affinity (< 1 nM) and did not bind other forms of amyloid beta. As mE8 and mE8c differ only in respect of Fc structure their target of binding, being Fab-mediated, is expected to be the same.

The company presented evidence to support the claim noted above to the effect that antibody that binds soluble as well as insoluble forms of amyloid beta, will be less effective at removing plaque than treatment targeted at an antigen present only in plaque. Donanemab and the murine surrogate mE8 antibody engaged deposited amyloid beta in brain after peripheral injection, whereas a comparator murine antibody, m3D6 antibody (anti-amyloid beta 1-X; murine IgG2b format) lacked notable in vivo target engagement. m3D6 is an antibody that binds both soluble and insoluble amyloid beta. This was published (DeMattos et al 2012 A plaque-specific antibody clears existing β-amyloid plaques in Alzheimer's disease mice. Neuron 76(5); 908-920 DOI: 10.1016/j.neuron.2012.10.029) in which it was argued that the lack of binding of m3D6 to plaque in transgenic PDAPP mice given the antibody was thought to be due to its saturation with soluble amyloid beta in the brains of these mice.

The company also presented evidence that Fc-mediated phagocytosis is how donanemab removes plaque. In in vitro testing using material from the brains of patients with Alzheimer's disease, the company showed an increased in clearance of amyloid beta from plaque on addition of microglial cells to the culture, in the presence of the murine surrogates, mE8 and mE8c. Clerance was greater with use of mE8c than with mE8 and the difference was attributed to the former possessing Fc-mediated effector functions whereas the latter lacked these. These data support the company's concept that donanemab, as a humanised IgG1, will perform more like mE8c than mE8 and so remove amyloid beta from established plaques.

In vivo testing was intended in transgenic PDAPP mice: to support this, the company reported results from in vitro testing on the brains of such mice in which it showed binding of mE8 to deposited plaque.

The company sought to show that use of donanemab would be expected, in human patients, to reduce plaque. It did this using the murine antibodies, mE8 and mE8c in PDAPP mice. These mice need to be elderly for this use, as they do not express significant amounts of amyloid beta protein when young - although some differences are described comparing between PDAPP mice and human patients, in this regard, they are similar. However, it is obvious that studies where dosing is started in mice of this age cannot be run in the longer term, due to the limits on life expectancy of mice at this age.

When such mice were given the murine surrogate antibodies over 3 months, mE8c significantly decreased deposited amyloid beta: m3D6 did not.

Comparing mE8 and mE8c, there was evidence of more extensive clearance of amyloid beta plaque in the brains of PDAPP mice given the surrogate with Fc-effector function (mE8c). This supports the company's proposal that for donanemab, use of an IgG1 construct in humans is important to obtain the best therapeutic response, as this depends on activation of phagocytic microglial cells to remove established plaque. A dose-response relationship was explored in PDAPP mice given Me8c with the conclusion that a dose of 12.5 mg/kg given once weekly had more activity to reduce established plaque than lower doses of 1.5 and 4 mg/kg.

In these analyses, reduction in plaque in key brain regions, the hippocampus and cerebral cortex were described. The hippocampus is particularly involved in storage of memories, memory retrieval and also the separate process of creation of new memories and Alzheimer's disease particularly affects these processes. However, there was no information presented in this dossier to the effect that removal of amyloid beta plaques led to a measurable effect on memory functions. Nor was there any investigation into electrophysiological processes that might associate with new memory formation, such as long term potentiation in hippocampal tissue.

mE8c did not prevent amyloid beta deposition when dosing was started in younger PDAPP mice.

No secondary pharmacodynamic studies were done. Safety pharmacology assessments were included in the general toxicity study in cynomolgus monkeys: no effects of donanemab were identified on the cardiovascular, neurological or respiratory systems.

The company also presented a study into risk of haemorrhage: this study showed that PDAPP mice given mE8c did not show any cerebral haemorrhage following 3 months of dosing.

In conclusion, despite that the company has not shown any benefit on memory or cognitive function in mice and such testing methods are available, this dataset is sufficient to support the concept that treatment with donanemab may impact on amyloid beta deposited in plaques.

III.3 Pharmacokinetics

Kinetics of donanemab were studied in cynomolgus monkeys dosed by subcutaneous and intravenous routes. Kinetic studies were also undertaken of mE8c, the murine surrogate of donanemab in PDAPP mice.

Enzyme-linked immunosorbent assays (ELISA) were used to measure donanemab in monkey serum and to measure mE8c in mouse plasma and serum. An ELISA method was validated to detect antibodies to donanemab in monkey serum and another in mouse serum.

This work was conducted in compliance with Good Laboratory Practice and had defined acceptance specifications of critical parameters that included system suitability, accuracy, precision, range of quantitation, selectivity, dilution linearity and analyte stability.

The following studies are discussed in this section:

1. **Study 8301447**- Serum Pharmacokinetics of LY3002813 in Cynomolgus Monkeys After Intravenous or Subcutaneous Administration: Comparison of 3 Material Lots
2. **Study 8237314**- Pharmacokinetics of LY3002813 in Cynomolgus Monkeys Following a Single Intravenous or Subcutaneous Dose of 1 mg/kg LY3002813
3. **Study 8253105 -** Serum and Plasma Exposure with Three Lots of mE8c (LSN3026818) in CD1 Mice Following a Single Subcutaneous Dose of 10 mg/kg

No studies were performed on distribution, metabolism, excretion or pharmacokinetic drug-drug interactions.

III.3.2 Absorption

Study 8237314- Pharmacokinetics of LY3002813 in Cynomolgus Monkeys Following a Single Intravenous or Subcutaneous Dose of 1 mg/kg LY3002813

Male cynomolgus monkeys, 2 – 5 kg, were given a single intravenous or subcutaneous dose of 1 mg/kg donanemab and blood was sampled at timepoints 0.25 (IV only), 0.5, 1, 6, 12, 24, 48, 72, 96, 120, 168, 240, 312, 384, 456, 528, 600 and 672 hours after dosing. There were 3 monkeys in each dose group. Serum was prepared and used to determine concentrations of donanemab using the antigen capture ELISA.

Results: After intravenous doing, the serum concentration profile was of a biphasic pattern of elimination (Figure 15, Table 2) with a terminal half-life of 173 hours (~7 days). After subcutaneous dosing, the maximum serum concentration was reached at a mean of ~64 hours after dosing and was 7.6 microg/ml with mean serum elimination half-life 161 hours (~7 days) (Figure 16, Table 3): absolute bioavailability by the subcutaneous route was ~91%.

Figure 15: Serum concentrations of LY3002813 after a single intravenous administration of 1 mg/kg to male cynomolgus monkeys. Data are from individual animals.

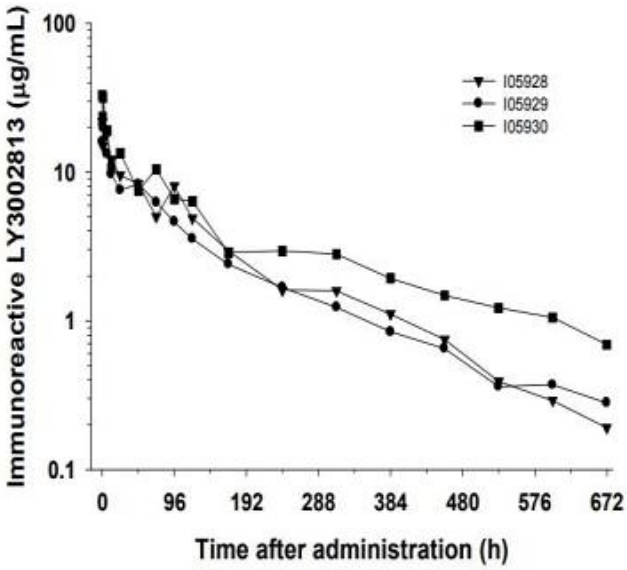


Table 2: Pharmacokinetic parameters of LY3002813 following intravenous administration of 1 mg/kg LY3002813 to male cynomolgus monkeys.

Parameter	I05928	I05929	I05930	Mean	SD	N
$AUC_{(0-672)}$ (h*µg/mL)	1720	1480	2390	1860	472	3
C_{max} µg/mL	21.8	20.9	32.9	25.2	6.7	3
t ½ β (h)	112	196	210	173	53	3
CL (mL/h/kg)	0.57	0.64	0.39	0.53	0.13	3
Vss (mL/kg)	83.1	98.6	75.7	85.8	11.7	3

Abbreviations: $AUC_{(0-672)}$, area under the serum concentration curve; C_{max}, observed maximum serum concentration; t1/2β, elimination half-life; CL, clearance; Vss, volume of distribution at steady state.

Figure 16: Serum concentrations of LY3002813 after a single subcutaneous administration of 1 mg/kg to male cynomolgus monkeys. Data are from individual animals.

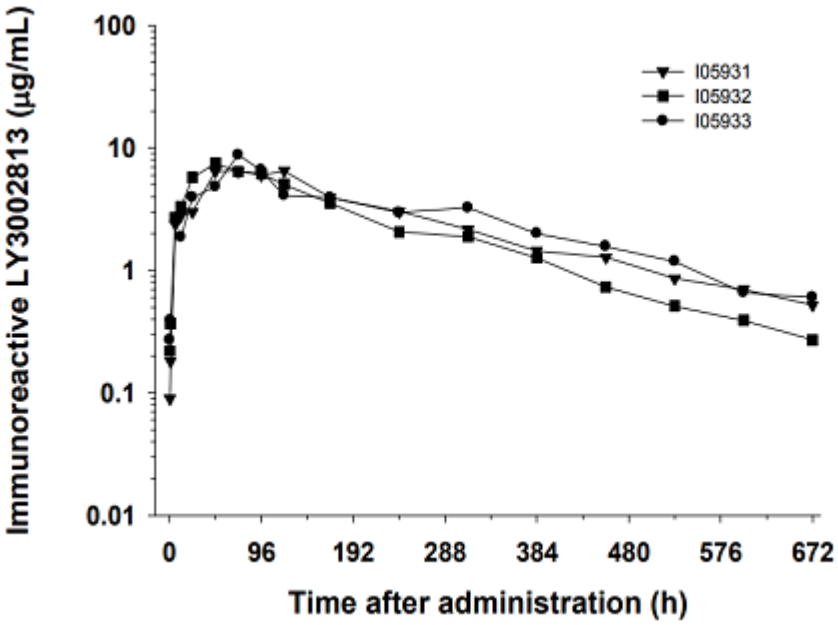


Table 3: Pharmacokinetic parameters of LY3002813 following subcutaneous administration of 1 mg/kg LY3002813 to male cynomolgus monkeys.

Parameter	I05931	I05932	I05933	Mean	SD	N
$AUC_{(0-672)}$ (h*µg/mL)	1720	1530	1830	1690	152	3
C_{max} µg/mL	6.5	7.5	8.8	7.6	1.2	3
T_{max} (h)	72	48	72	64	14	3
t ½ β (h)	160	180	143	161	19	3
CL/F (mL/h/kg)	0.58	0.65	0.55	0.59	0.05	3

Abbreviations: $AUC_{(0-672)}$, area under the serum concentration curve; t1/2β; elimination half-life; C_{max}, maximum serum concentration; T_{max}, time to maximum serum concentration; CL/F, clearance/bioavailability or apparent clearance.

Study 8301447- Serum Pharmacokinetics of LY3002813 in Cynomolgus Monkeys After Intravenous or Subcutaneous Administration: Comparison of 3 Material Lots

In study 8301447, kinetics of three different lots of donanemab were compared after single intravenous or subcutaneous dosing to cynomolgus monkeys. Males were given a single intravenous dose of 1 mg/kg donanemab from each batch and blood was sampled at timepoints 0.25 (IV only), 0.5, 1, 6, 12, 24, 48, 72, 96, 168, 240, 408, 504 and 672 hours after dosing. There were 3 monkeys in each dose group. Serum was prepared and used to determine concentrations of donanemab by ELISA.

Pharmacokinetic parameters were determined based on the blood concentration data generated. In addition, one of the batches was given at 1 mg/kg by subcutaneous injection to 3 further monkeys and blood sampled as described for after intravenous dosing.

Results: Results are given in Table 4 below. The kinetics of donanemab from each lot were generally similar with elimination half-lives 168 - 192 hours and C_{max} values of ~19-23 µg/ml and AUC0-672h of 1710-1900 µghr/ml.

Comparing kinetics of lot C2: EL01504-009-API after intravenous and after subcutaneous dosing, the elimination half-life was similar (~10 days) and mean AUC was similar: bioavailability was estimated at 100%.

No testing for antibody to donanemab was done but the report noted that pharmacokinetic profile for one monkey given Formulation C2 by the intravenous roue showed a notable decrease in measured serum concentration of donanemab at the 504-hour time point compared to the two others in the same group.

This study identified no difference in kinetics of donanemab in monkeys for these lots.

Table 4: Mean serum concentrations (ng/mL) of LY3002813 in Cynomolgus Monkey after a single 1 mg/kg by the IV or SC routes.

Route	Group	C_0 (µg/mL)	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-672} (hr•µg/mL)	$AUC_{0-\infty}$ (hr•µg/mL)	Cl or Cl/F (mL/h/kg)	V (mL/kg)	$t_{1/2}$ (hr)
IV	1 (T)	21.2	20.9	1.0	1900	2080	0.49	119	192
IV	2 (C1)	24.4	23.1	0.5	1870	1980	0.51	107	168
IV	3 (C2)	20.2	19.3	0.5	1710	1830	0.55	114	179
SC	4 (C2)	NC	6.7	48.0	1910	2200	0.49	156	233

Abbreviations: AUC_{0-672} = area under the curve from time 0 to 672 hr, $AUC_{0-\infty}$ = area under the curve from time 0 to infinity, Cl or Cl/F = clearance, C_0 = concentration extrapolated to time 0 hour, C_{max} = maximum concentration, $t_{1/2}$ = elimination half-life, T_{max} = time at maximum concentration, V = volume of distribution.

No studies were performed on distribution, metabolism, excretion or pharmacokinetic drug-drug interactions.

Study 8253105: Serum and Plasma Exposure with Three Lots of mE8c (LSN3026818) in CD1 Mice Following a Single Subcutaneous Dose of 10 mg/kg

In this study, kinetics of three lots of mE8c were compared in mice. mE8c is a murine antibody directed against an amyloid beta peptide species in which the first two amino-acids are absent, and the third amino acid is modified as a pyro-glutamate (Aβp3-X): it is the murine IgG2a surrogate of donanemab and was used in mouse pharmacology and toxicology studies.

In the general toxicity study 504299 (discussed later in the Toxicology section of this report), serum concentrations of mE8c were substantially lower than plasma concentrations of mE8c determined in pharmacology studies. The purpose of PK study 8253105 was to evaluate whether test article lot to lot differences or collection of samples as serum versus plasma had an effect on measurable levels of mE8c and if this could account for differences in exposure across studies.

Briefly, CD1 mice were given a single dose of 10 mg/kg mE8c supplied as a 26.6 mg/mL stock solution, 27.0 mg/mL stock solution or 11.7 mg/mL stock solution.

Samples were collected from 4 mice per timepoint at 24, 48, 96 and 168 hours after SC dosing, and processed as serum. An additional 4 animals were dosed and at 48 hours samples collected and processed as plasma. For each matrix, the assay validation range (lower and upper limits of quantification, LLOQ, ULOQ) was 10-500 ng/ml. Samples exceeding the ULOQ were diluted in blank matrix with a dilutional range up to 20,480-fold validated.

Results: In serum, exposure to mE8c was comparable across the groups (Table 5). Plasma, concentrations of mE8c at the 48-hour timepoint were also similar across all dose groups (Table 6). However, comparing the 48-hour timepoint between the two matrices, plasma mE8c concentrations were 26 - 36 fold higher than serum concentrations (Table 6). In assay validation experiments, mE8c demonstrated stability when incubated to mouse serum at room temperature for up to 24 hours, indicating that the loss of recovery was a consequence of processing from whole blood to serum. The company concluded that mE8c shows loss of recovery when processed as serum from whole blood samples.

Table 5: Summary of mean serum exposure parameters for mE8c in male CD1 mice following single subcutaneous dose of 10 mg/kg.

Group	Lot	Cmax (ng/mL)	$AUC_{0\ to\ 336h}$ (ng*hr/mL)
1	EL01125-032-API	1783	566304
2	EL01097-154-API	2413	536984
3	15499-054	2493	623606

Abbreviations: Cmax, maximum concentration; AUC, area under the curve. Exposure parameters were derived from mean concentrations obtained from 4 animals per group per timepoint.

Table 6: Summary of mean serum or plasma concentrations following administration of mE8c in male CD1 mice as a single subcutaneous dose of 10 mg/kg.

		Time (h)						
Group		0 Serum	24 Serum	48 Plasma	48 Serum	96 Serum	168 Serum	336 Serum
1	Mean mE8C concentration (ng/mL)	0*	1683	53867	1705	1770	1738	1783
	SD	0	409	4554	186	488	476	82
2	Mean mE8C concentration (ng/mL)	ND	2413	62067	1745	1436	1645	1570
	SD	ND	626	6691	714	817	1205	385
3	Mean mE8C concentration (ng/mL)	ND	2460	63733	2493	1928	1655	1928
	SD	ND	458	6372	782	276	193	401

*<BQL (10 ng/mL); value of zero was used for calculations. ND; not determined.

II.3.3 Conclusions on pharmacokinetics

Enzyme-linked immunosorbent assays (ELISA) were used to measure donanemab in monkey serum and to measure the murine surrogate antibody mE8c in mouse plasma and serum. An ELISA method was validated to detect antibodies to donanemab in monkey serum. These methods were each judged to be suitable.

The totality of kinetic data for donanemab include those summarised above as well as toxicokinetic data generated from monkeys in general toxicity studies.

As a single dose, the intravenous use of donanemab indicated a biphasic elimination profile with the mean terminal elimination half-life of ~173 hours in male cynomolgus monkeys. At a dose of 1 mg/kg subcutaneously, the T_{max} was estimated at 64 hours and estimated bioavailability was high at ~91- 100%. On repeated intravenous dosing of 1, 10 or 100 mg/kg with dosing once every week over 6 weeks, exposure values after the last dose were not more than ~2.0-fold those after the first dosing indicating a minor degree of accumulation. There were no gender differences in exposure.

Antibodies to donanemab were detected in some animals on repeated dosing but did not affect the exposure to donanemab.

Overall, these studies described a profile expected for a humanised antibody given to cynomolgus monkeys where there was no target engagement.

Suitable assays were also developed to measure mE8C in mouse blood. There was a notable difference in antibody concentration in plasma and in serum and it was determined that loss occurred on processing whole blood to serum. For this reason it is not appropriate to compare exposure in different mouse studies where drug was measured in plasma with those where drug was measured in serum.

Distribution studies are not required. As a biological product, this product is expected to be degraded to small peptides and amino acids and studies of routes of metabolism are not required.

Direct drug-drug kinetic interactions are not anticipated because this product is not metabolised by cytochrome P450 enzymes and it is not a substrate for transporter proteins. Indirect interactions whereby this product might influence expression of these enzymes are not anticipated.

III.4 Toxicology

The following studies are discussed in this section:

1. **Study 8242713** - Repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys given LY3002813 by intravenous injection once weekly for 6 weeks with a 3-month recovery phase
2. **Study 8222-743 -** Chronic pharmacology/toxicity study in aged female PDAPP mice given weekly subcutaneous doses of mE8 Derivative C (murine analog of LY3002813) for six months
3. **Study 504531 -** Repeat-dose toxicity and exposure study in PDAPP mice given LSN3026818, mE8 Derivative c (mE8c, murine analog of LY3002813) by subcutaneous injection once weekly for 6 months
4. **Study 504299 -** Repeat-dose toxicity and exposure study in PDAPP mice given LSN3026818, mE8 Derivative c (mE8c, murine analog of LY3002813) by subcutaneous injection once weekly for 6 weeks
5. **Study 20008867 -** Tissue cross-reactivity of LY3002813 with human and cynomolgus monkey tissues *ex vivo*
6. **Study MB135 -** Cerebral microhaemorrhage and neuropathology study in aged PDAPP mice given LSN3026818, mE8 Derivative C (mE8c, murine analog of LY3002813), by intraperitoneal injections weekly for 3 months

In Study 8242713, the monkeys were not pharmacologically responsive as at the age used in the study as they do not have any amyloid beta in their brains. Thus, the study assessed the potential for off-target toxicity.

On-target effects were evaluated in various hazard identification studies up to 6 months in duration in a mouse model of disease (PDAPP transgenic mice) with a murine surrogate molecule (mE8c).

All studies conducted in monkeys and mice included an expanded neuropathologic evaluation of the brain.

The drug product is presented as either a lyophilisate of 350 mg/vial, or as a solution of 700 mg in a vial in each case for reconstitution in 20 ml of sterile water for injection to a concentration of 17.5 or of 35 mg/ml and pH 6.0: it should be used within 24 hours of reconstitution. The vehicle (10 mM citrate, 150 mM sodium chloride, and 0.02% polysorbate 80 in Sterile Water for Injection) used in the 6-week monkey toxicology study contained the same buffer, surfactant, pH and isotonicity as the clinical formulation.

Tissue cross-reactivity studies

Tissue cross-reactivity studies evaluated binding of donanemab to human and cynomolgus monkey tissues (report 20008867). Binding of donanemab was detected using biotinylated anti-human antibody with visualisation using an avidin-biotin-horseradish peroxidase complex and chromogenic substrate (diaminobenzidine). Testing was done at donanemab concentrations of 5 and 25 microg/ml.

As a positive control, human brain known to contain amyloid beta was used to show that binding of donanemab could be detected. Brain tissue from PDAPP transgenic mice was also used as a positive tissue control. Human cerebellum was used as a negative control tissue. Tissue sections were stained with an antibody to CD31 platelet endothelial cell adhesion molecule (PECAM-1) to confirm that they were suitable for use. A biotinylated murine anti-amyloid beta antibody was used. Finally, a non-specific antibody was also used to confirm that it did not detect binding to amyloid beta.

Tissues were sourced from 3 different human donors. It was noted that there may have been many more donors, but each human tissue was tested in samples from 3 different donors. The tissues used are shown below with a similar panel tested from cynomolgus monkeys.

Human Tissue (Normal) from Three (3) Healthy Separate Individuals

- Adrenal
- Bladder
- Blood[1]
- Bone Marrow
- Breast
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium (aorta)[1]
- Eye
- Fallopian Tube
- Gastrointestinal Tract[2]
- Heart
- Kidney (glomerulus)[3]
- Kidney (tubule)[3]
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid
- Parotid Gland (salivary gland)
- Peripheral Nerve
- Pituitary
- Placenta
- Prostate
- Skin
- Spinal Cord
- Stomach
- Spleen
- Striated Muscle
- Testis
- Thymus
- Thyroid
- Tonsil
- Ureter
- Uterus (cervix)
- Uterus (endometrium)

[1] Evaluated from all tissues where present
[2] Gastrointestinal Tract was evaluated in a sample of small intestine.
[3] Kidney (glomerulus) and Kidney (tubule) were both evaluated in the same tissue sample.

Staining intensity was rated on a 5-point score, from none, through light to marked: staining frequency was also recorded on a 5-point scale, from none, through rare to frequent.

Results: Staining of amyloid plaques was evident, as expected. In humans, there was specific staining of lymphocytes in multiple tissues, although this was intracellular. In monkeys, there was also specific staining of lymphocytes in multiple tissues. Intracellular binding is considered of no significance here as, in life, the antibody is not expected to cross the cell membrane. There was also staining of myelin in the peripheral nerve, of nuclei in a variety of tissues and of cells in the thyroid, fallopian tubes and, in one sample only, of the pituitary. However, no binding to membranal targets was identified in either humans or monkeys.

Single dose toxicity

No single dose toxicity studies were done.

Repeat-dose toxicity

The company supplied one repeat dose general toxicity study with donanemab (8242713) and several in mice given the murine surrogate.

In study 8242713, cynomolgus monkeys were given intravenous doses of donanemab once weekly over 6 weeks with, in some monkeys, a 3-month follow-up period after the last dose. Monkeys were aged 2 to 4 years old and they weighed 2.3-3.5 kg: there were 6 (control, high dose groups) or 3 (low, mid dose groups) male and female monkeys in each group. Donanemab was given at doses of 0, 1, 10 or 100 mg/kg.

Monkeys of this age are likely to be sexually immature and the report notes that this was so for males and it was not possible to evaluate effects of donanemab on spermatogenesis. Evaluations included of clinical signs, body weight, food consumption, neurological examinations, respiratory and body temperature measurements, ophthalmological and electrocardiogram (ECG) evaluations and clinical and anatomical pathology; there were detailed neuropathological evaluations. Blood samples were collected for toxicokinetic and immunogenicity evaluations.

Results: Analyses of dosing solutions confirmed that this was at the concentration expected throughout the study: this was measured at 52.2 mg/ml. The intended doses were delivered. Dosing was well tolerated and there were no unscheduled deaths and no notable clinical signs of toxicity. Across all the measures in the study, monkeys given donanemab showed no findings indicated notable differences from controls or from historical background values for normal monkeys, with the exception that globulin increased, especially at the highest dose this is likely the presence of administered donanemab). Consequently, the no observed adverse effect level (NOAEL) was set at 100 mg/kg, the highest dose used. At this dose at the end of dosing, on day 36, exposure was quantified at 2593 microg/ml (Cmax) and 142219 microgh/ml (AUC0-166), averaged for males and females.

One control monkey had measurable donanemab (9.67 microg/ml) in serum, 48 hours after dosing. This was not explained but as a single instance, it was judged not to indicate that the monkey had been given the drug.

Antibodies to donanemab were detected in 1 monkey from groups given 0, 1 and 10 mg/kg and from 4 monkeys given 100 mg/kg. Of 36 monkeys in the study, 7 tested positive for antibody.

In safety pharmacology evaluations, no effects were noted on PR interval, QRS duration, QT or corrected-QT intervals and no rhythm abnormalities or qualitative ECG changes were attributed to donanemab. In-life there were no abnormalities noted in haematology or analyses relating to coagulation, blood cells or clinical chemistry. At the injection sites, evaluations were unremarkable with no indications of irritation seen.

Each brain was sectioned longitudinally and histological sections prepared from the following sites: immediately rostral to the optic chiasma, at the level of infundibulum, rostral to the thalamus, rostral pons and thalamus, including the hippocampus, ventral and dorsal medulla oblongata and cerebellum and the middle of the cerebellum. No findings of toxicity were identified on examination of these tissues.

The company noted that monkeys are not pharmacologically relevant and this study assessed only off-target toxicity. On-target toxicity was assessed in transgenic mice given the murine surrogate.

4 female monkeys were recorded as having vomited during the dosing phase, all from the high dose group. This did not occur in males at any dose and no significance is attributed to this.

Table 7: Summary of repeat-dose toxicity studies with LY3002813.

Study Number Live Phase Dates	Species Strain No./Sex/Group Age	Doses (mg/kg/week) Route Duration	Parameters Evaluated	Noteworthy Findings
8242713 April-August 2011	Monkey Cynomolgus 3 Main, 3 Recovery 2-4 years	0[a], 1, 10, 100 Intravenous 6 weeks with 3-month recovery	Survival, BW, FC, clin signs, phys, ophthal, ECG, clin path[b], path[c], TK, immuno	None. NOEL = 100 mg/kg; Day 36 C_{max} = 2593.33 µg /mL, $AUC_{(0-166)}$ = 142219.02 µg•hr/mL (average of male and female).

Abbreviations: $AUC_{(0-166)}$ = area under the concentration-time curve from time 0 to 166 hours postdose; BW = body weight; clin = clinical; C_{max} = maximum observed serum concentration; ECG = electrocardiogram; FC = food consumption; hr = hour; immuno = immunogenicity, NOEL = no-observed-effect level; No. = number; ophthal = ophthalmic examinations; path = pathology; phys = physical examinations; TK = toxicokinetics.

[a] Vehicle control group. Vehicle = 10 mM sodium citrate, 150 mM sodium chloride, and 0.02% (w/v) polysorbate 80 prepared in Sterile Water for Injection, United States Pharmacopeia (pH 6.0 ± 0.2).

[b] Hematology, clinical chemistry, and urinalysis.

[c] Organ weights, gross pathology, and histopathology, including an expanded neuropathology evaluation.

Table 8: Summary of non-clinical safety pharmacology studies with LY3002813.

Organ Systems Evaluated Study Number Live Phase Dates	Species Strain Gender, No./Group	Doses (mg/kg/week)[a] Route	Parameters Evaluated	Noteworthy Findings
Cardiovascular Effects 8242713 April-August 2011	Monkey Cynomolgus 3/sex (1, 10 mg/kg) 6/sex (0, 100 mg/kg)	0[b], 1, 10, 100 Intravenous	Quantitative evaluation of ECG measurements (heart rate, PR, QT, QTc, and QRS intervals) collected prior to the first dose, Day 8, and Day 29. Qualitative evaluation for abnormal waveform morphology and arrhythmias.	None. NOEL = 100 mg/kg
Central Nervous System Effects 8242713 April-August 2011	Monkey Cynomolgus 3/sex (1, 10 mg/kg) 6/sex (0, 100 mg/kg)	0[b], 1, 10, 100 Intravenous	Neurologic examinations and body temperature prior to the first dose, and at 1, 6, 12, 24, 72, and 150 hr after the first dose; and prior to dosing and 1 and 24 hr post dose on Days 22 and 36.	None. NOEL = 100 mg/kg
Respiratory Effects 8242713 April-August 2011	Monkey Cynomolgus 3/sex (1, 10 mg/kg) 6/sex (0, 100 mg/kg)	0[b], 1, 10, 100 Intravenous	Qualitative respiratory assessment (depth) and quantitative estimate of respiration (breaths/minute) prior to the first dose, and at 1, 6, 12, 24, 72 and 150 hr after the first dose; prior to dosing and 1 and 24 hr post dose on Days 22 and 36.	None. NOEL = 100 mg/kg

Abbreviations: ECG = electrocardiogram; hr = hour; No. = number; NOEL = no-observed-effect level; QTc = corrected QT interval; PR = pulse rate.

[a] Once-weekly dosing for 6 weeks.

[b] Vehicle control group. Vehicle = 10 mM sodium citrate, 150 mM sodium chloride, and 0.02% (w/v) polysorbate 80 prepared in Sterile Water for Injection, United States Pharmacopeia (pH 6.0 ± 0.2).

Four studies were done in PDAPP mice, one with dosing over 6 weeks (report 504299) and two with dosing over 6 months (504531 and 8222743). Whereas the first two studies were in compliance with GLP, the second 6 month study was not intended as a GLP-compliant study.

Table 9: Summary of the toxicity studies in mice.

Study Number Live Phase Dates	Species Strain No./Sex/Group Age	Doses (mg/kg/week) Route Duration	Parameters Evaluated	Noteworthy Findings
504299 April-May 2011	Mouse PDAPP-6042M 9-10 12-15 months	0[a], 10, 30, 100 Subcutaneous 6 weeks	Survival, BW, FC, clin signs, ophthal, clin path[b], path[c], exposure	None. NOEL = 100 mg/kg; mE8c serum conc at 48 hr after last dose = 272.1 µg/mL.[d]
8222-743 non-GLP July 2009- January 2010	Mouse PDAPP-6042T 15 F (tox) 16 months	0[e], 1.5, 4, 12.5 Subcutaneous 6 months	Clin path[b], path[c], exposure	None. NOEL = 12.5 mg/kg; mE8c plasma conc at 72 hr after last dose = 234.6 µg/mL.
504531[f] August 2011- January 2012	Mouse PDAPP-6042M 19-20 12-15 months	0[a], 30, 100 Subcutaneous 6 months	Survival, BW, FC, clin signs, clin path[b], path[c], exposure	NOEL = 100 mg/kg; mE8c plasma conc in males on Day 151/152 = 463775 ng/mL
MB135 non-GLP February-May 2008	Mouse PDAPP-1683T 23-27 F, 15 M 23-25 months	0[e], 12.5 mE8c, 12.5 mE8, 12.5 3D6[g] Intraperitoneal 3 months	Microhemorrhage, neuropathology, exposure	No increase in microhemorrhage. mE8c plasma conc at 72 hr after last dose = 82.16 µg/mL.

Study 504299

In the first study, (GLP), mice aged 12 – 15 months old and weighing between 19.8 – 32.9 g at study start, were dosed by subcutaneous injection with mE8c, a murine surrogate of donanemab, at doses of 0 (saline), 10, 30 or 100 mg/kg. Dosing was on study days 1, 8, 15, 22, 29, 35 and necropsy was scheduled on day 43. There were 19 or 20 mice in each dose group (9 or 10 males and females). Additional mice were used as satellites for measuring exposure in blood taken from mice on days 1 and 36 and again at necropsy, scheduled on day 43. Serum samples were analysed by ELISA to quantify mE8c with a lower limit of quantification of 10.0 ng/ml.

Mice were observed for clinical condition, body weight, food consumption, ophthalmological examinations, haematology, and clinical biochemistry and on day 43 were killed and organs weighed and tissues prepared for histological evaluations. Results: There were a number of unscheduled deaths in this study. However, as these mice were elderly at the start of the study, this was expected.

In total, 19 mice, across all the dose groups, did not reach the scheduled timepoint for postmortem evaluations, with some (13) found dead and others (6) killed to prevent ongoing suffering: - these mice had shown signs such as thinness, cold to the touch, decreased activity skin pallor, dehydration and laboured breathing.

The deaths occurred on study days 2, 3, 6, 7, 12, 13, 15 20, 21, 22, 23, 25, 26, 30, 33, 34, 36 and 43 and on analysis were mostly associated with malignant neoplasms of haematolymphatic tissue with the presence of metastases in liver, spleen, bone marrow and/or lymph nodes. In the dose groups, 0, 10, 30 and 100 mg/kg the number of deaths were 7, 5, 4 and 3 respectively.

There were no effects identified on measures of clinical signs, body weights or food consumption. On ophthalmological evaluations there were age-related changes (e.g. corneal opacities) but no effect of treatment was recognised. Haematological and clinical biochemical changes were noted in those mice that developed neoplastic proliferation but this was not judged an effect of m8Ec. Post-mortem evaluations were unremarkable with no effect of m8Ec recognised on measures of organ weights or on pathological evaluations. In males, normal progression of the spermatogenic cycle and expected cell associations and cell proportions in the various stages of spermatogenesis were present.

Plaques were seen in the brains of most mice, often in the hippocampus and overlying cerebral cortex. The company concluded that the NOEL in this study was 100 mg/kg with no toxicity of mE8c identified. m8Ec was detected in one serum samples from a control mouse which was on day 43. This was measured at 12.3 ng/ml, just above the 10.0 ng/ml lower limit of quantification. It was quantifiable in all samples taken from treated mice except for one sample from a mouse at 48 hours after the first dose. High-inter animal variability was noted. However, it was detectable at all timepoints, including 7 days after the last dose. Exposure increased with dose and with notable accumulation of 5 – 10 fold between dose 1 and dose 6.

Study 504531

In study 504531, m8Ec was given subcutaneously once weekly for 6 months to PDAPP mice aged 12 – 15 months old at study start and weighing 20.9 - 37.5 g. Doses were 0 (saline), 30 or 100 mg/kg. Dosing was intended for a period of 6 months; however, mice died during the study and the decision was taken to continue dosing in each group until there were 5 male or 5 female mice left alive and then the remaining mice were killed within 2 days. The study ran to days 141 in females and 151 in males. There were 38 or 40 mice in each dose group (19 or 20 males and females). Additional mice were used as satellites for measuring exposure; however, Serum samples were analysed by ELISA to quantify mE8c with a lower limit of quantification of 10.0 ng/ml.

Mice were observed for clinical condition, body weight, food consumption, ophthalmological examinations, haematology, and clinical biochemistry and on day 140/141 (females) and day 150/151 (males) mice were killed and organs weighed and tissues prepared for histological evaluations.

Results: There were many unscheduled deaths in this study. In total, of 116 mice in the study, 70 died early, with 55 were found dead and 15 killed to prevent ongoing suffering. Arising from this the study was altered as explained above, to keep each dose group going until 5 male or 5 female mice remained. As in the 6 week study, these deaths were mostly associated with malignant neoplasms of haematolymphatic tissue with the presence of metastases in liver, spleen, bone marrow and/or lymph nodes. In the dose groups, 0, 30 and 100 mg/kg the number of deaths were 27, 18 and 25 respectively with approximately equal numbers of males and females dying.

There were no effects identified as toxicity arising from, use of mE8c on measures of clinical signs, body weights or food consumption or the other measures evaluated over the course of this study. All the changes seen were identified as either due to multicentric lymphoma or, if not such, were considered expected in elderly PDAPP mice judged an effect of m8Ec. At post-mortem, no effects were noted of mE8c on organ weights or on pathological evaluations.

In males, normal progression of the spermatogenic cycle and expected cell associations and cell proportions in the various stages of spermatogenesis were present.

Plaques were seen in the brains of most mice, often in the hippocampus and overlying cerebral cortex. These were not quantified: plaque burden was not evaluated in this study.

The company concluded that the NOEL in this study was 100 mg/kg. At this dose the mean exposure was 463.8 microg/ml.

Study 8222-743

Study 8222-743 was a further general toxicity study of mE8C in female PDAPP mice. This study was not intended to be in compliance with Good Laboratory Practice.

Mice were allocated to treatment with mE8c at doses of 1.5, 4 or 12 mg/kg or a control who were given a non-specific murine IgG2a antibody; dosing was once weekly subcutaneously over 6 months. There were initially 30 mice in each group and they were aged 16 months at the start of the study. The top dose in this study was selected as it was used in the 3 month study assessing microhaemorrhages. At 72 hours after the last dose, mice were killed and blood taken for analysis of plasma concentrations of mE8c by ELISA and also for haematological and clinical chemical analyses. At this timepoint too, necropsies were planned with organs weighed and tissues collected for gross and microscopic pathological analysis.

In this study there were 7 unscheduled deaths of 30 mice in each group, except for the top dose group, where 6 died. Deaths occurred on study days 93, 140, 150, 159, 173 and 179 in controls and between days 88-163, 93-179 and days 29-159 in dose groups given 1.5, 4 and 12.5 mg/kg respectively. In each case, the company attributed these deaths to the age of the mice; on the proportion of mice that did die early, the company stated that this is within the expected spontaneous rate of death of such mice of this age. From the surviving mice, 15 from each group were selected and toxicological evaluations were carried out on them. There were no changes identified as related to mE8c in haematology, clinical chemistry, organ weight, macroscopic or microscopic endpoints including in the neuropathology assessment. Effects that were seen were attributed to naturally occurring disease processes occurring in this age of mice. The NOAEL was set at 12.5 mg/kg. The mean concentration of antibody in plasma as quantified by ELISA were, for the dose groups of 1.5, 4 and 12.5 mg/kg, 27.8 +/- 2.6, 62.5 +/- 5.7 and 234.6 +/- 20.9 microg/ml. Thus for the 8.3-fold dose increase between 1.5 and 12.5 mg/kg there was an increase of ~8.4 fold in plasma mE8c concentration.

Study Mb135

A further study was done with the specific aim to evaluate cerebral microhaemorrhage in PDAPP mice given the murine antibodies mE8c or mE8 (report Mb135). This was an exploratory study, not intended to be in compliance with GLP.

mE8c is an IgG2a construct and mE8 is an IgG1 construct: in mice, the IgG2a construct retain more Fc-receptor mediated activity than does the IgG1 construct. Further mice served as controls and were given a control IgG2a antibody or a further antibody, 3D6, that is an IgG2b construct targeted against an epitope in the amino-terminus of the amyloid beta peptide, acting in this study as a positive control.

Analyses of plaque material from PDAPP mice has identified the amyloid peptide N3pGlu (that is targeted by donanemab) to constitute~0.1-1% of plaque material. APP transgenic mice given certain antibodies to amyloid beta showed an increased in cerebral amyloid angiopathy-related microhaemorrhage: these mice have amyloid beta deposited around cerebral blood vessels.

In this study, male and female PDAPP mice were allocated to doses of 0 or 12.5 mg/kg of either antibody, mE8c, mE8 or 3D6 and were dosed intraperitoneally once weekly for 3 months from the age of 23-24 months. 72 hours after the final dose, blood from mice was analysed to detect each of the antibodies used in the study to confirm exposure in plasma. This used an antigen capture ELISA method with plates coated with N3pG peptide to capture each of mE8 and mE8c or use of full length amyloid beta 1-42 peptide to capture 3D6. Bound murine antibody was detected by use of anti-murine horseradish peroxidase and developed with the chromagen, tetramethylbenzidine. These assays had coefficients of variations of <20% and were judged sufficient for their use in this study.

At the end of dosing, mice were killed and their brains removed and prepared for analyses including staining with Prussian blue to identify haemosiderin-laden phagocytes (siderophages) and with hematoxylin and eosin for neuropathological evaluations. Specific evaluations were made of evidence for microhaemorrhages and neurodegeneration.

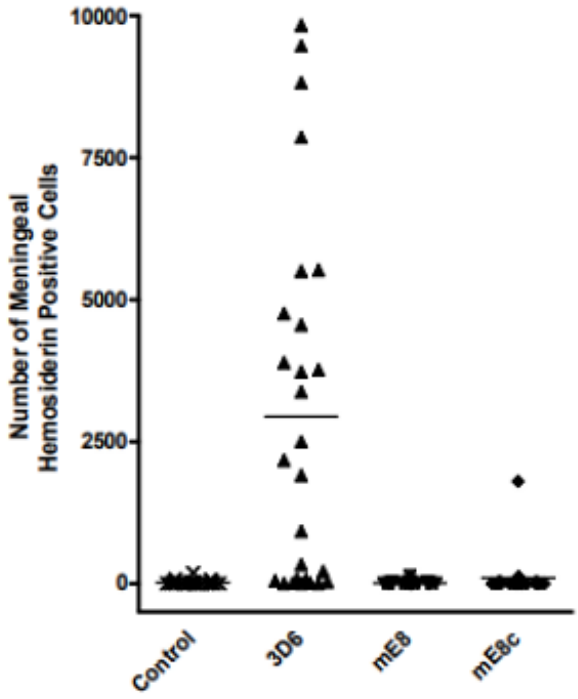
Results: In a dosing misadventure, 3 mice intended to be in the group given mE8c were given mE8 for their first dose and were then given their intended treatment of mED8c.

There were a number of unscheduled deaths: according to the company, these were not unexpected of mice at this age and the company attributed none of these to the treatments.

In plasma at 72 hours after their last dose, the amount of each antibody was determined for each of mE8c, mE8 and 3D6 at 82.16, 107.86 and 82.87 microg/ml, respectively.

Treatment of these aged PDAPP mice for 3 months with either mE8 or mE8c did not exacerbate microhaemorrhages: the Perls'-stain positive cell count for either of these anti-Aβp3-x antibodies was not different from the concurrent IgG1 control (Figure 17). 3D6, which was previously shown to exacerbate microhaemorrhage in these mice in a published study, did increase microhaemorrhage.

Figure 17: Prevalence of CAA-associated microhaemorrhage in aged PDAPP mice chronically treated with Aβ antibodies.



In neuropathological examinations, no histopathological changes attributed to treatments were identified in hemicoronal sections of brains extending from a level approximately even with, or just rostral to, the lateral septal nucleus to the level of the rostral portion of the hippocampus. Perivascular infiltrates of mononuclear leukocytes, especially lymphocytes, were occasionally found in the meninges and/or parenchyma of brains from all groups except the young procedural control mice but the infiltrates were consistently of minimal severity and frequency did not differ between groups. One occurrence of minimal meningeal vascular wall thickening found in one 3D6-treated mouse was not unexpected as a background change. There was no evidence of increased neurodegeneration with any treatment.

The company concluded that the 3D6 antibody (anti-amyloid beta amino-terminal antibody anti-Aβ1-x, IgG2b) increased CAA-related microhaemorrhage even in the absence of plaque lowering. Neither mE8 (anti-Aβp3-x, IgG1) or mE8c (anti-Aβp3-x, IgG2a) increased microhaemorrhages at a dose that lowered deposited amyloid beta. Neuropathological evaluation showed no increase in neurodegeneration.

Toxicokinetics

Table 10 gives the kinetic data of donanemab in monkeys in the general toxicity study (8242713). Exposure increased across the dose range 1 – 10 – 100 mg/kg in approximate proportion with dose with little difference (<2-fold) between males and females. Values were higher on day 36, the last day of dosing, than on day 1 but again <2-fold, indicating little accumulation on repeated dosing. Steady state was reached by day 22.

In terms of antibodies, only a minority of monkeys tested positive, 7 out of 36. In one male and one female both at 100 mg/kg there was an altered pattern of clearance of donanemab and these two had the highest antibody titres. In the remaining monkeys, the elimination half-life was estimated at ~295 hours.

Table 10: Mean serum toxicokinetic data summary.

Parameter		Administered Dose (mg LY3002813/kg)					
		1		10		100	
	Sex	M	F	M	F	M	F
LY3002813							
Day 1							
C_0 (ng/mL)[a]		17460	15996	213202	194814	2459760	3006627
SD C_0 (ng/mL)		2848	3033	20173	24667	521094	652051
C_{max} (ng/mL)[b]		17133	15700	201667	184000	2265000	2708333
SD C_{max} (ng/mL)		2663	2851	17156	21071	431451	537789
$AUC_{0\text{-}166hr}$ (ng·hr/mL)		1063667	1058648	10962401	10215974	87063713	94603147
SD $AUC_{0\text{-}166hr}$ (ng·hr/mL)		107495	95108	645605	1237133	7993920	15233768
Day 36							
C_0 (ng/mL)[a]		27668	25764	251862	277988	2797149	2676595
SD C_0 (ng/mL)		5914	3722	16453	23749	936259	414127
C_{max} (ng/mL)[b]		26500	24667	255000	264333	2651667	2535000
SD C_{max} (ng/mL)		5400	3769	13892	20817	797807	365226
$AUC_{0\text{-}166hr}$ (ng·hr/mL)		1954611	1616119	20861064	17607861	138630908	145807131
SD $AUC_{0\text{-}166hr}$ (ng·hr/mL)		535656	621288	834888	2658868	21377571	20309929

F = Female; M = Male; SD = Standard deviation.
Note: Values represent three animals/sex/group at 1 and 10 mg/kg and six animals/sex/group at 100 mg/kg.
a Back extrapolated concentration at time 0.
b Observed C_{max}.

Interspecies comparison

The pharmacological target of donanemab is only present in deposited amyloid plaque which is presumed not to be present in the brains of young adults, whether humans or animals. Older animals, including cynomolgus monkeys, do develop amyloid plaques but this is only likely to be present in monkeys aged at least 20 years old: studies in such monkeys are not considered feasible. Younger monkeys aged 2 - 4 years old were used in the general toxicity study 8242713 with dosing over 6 weeks.

As shown in Table 11, the estimated exposure to donanemab in monkeys in this study was almost 10-fold higher by measure of either Cmax or AUC, compared to that expected in human given donanemab at 20 mg/kg (~1400 mg).

Given that mE8C is a different antibody to donanemab, exposure in mice in toxicity studies where it was used is not compared with that intended in humans.

Table 11: Margin of safety for intravenous administration of donanemab based on administered dose and steady state exposure.

	Dose (mg/kg/mo)	**Dose Multiple[a]**	**$AUC_{0\text{-}t,ss}$ (µg•hr/mL)**	**C_{ss} (µg/mL)**	**Margin of Safety[a]**
Human[b]	20	20X	58000	87.7	9.7X
Monkey NOEL[c]	400[c]	–	142000	855	–

Abbreviations: a Dose multiple is dose in animals/dose in humans based on mg/kg. Dosing frequency in monkeys was once per week and in humans was once per month. b 1400 mg is ~20 mg/kg. AUC0-30days,ss µghr/ml; Caverage,ss; is from the AACG Population PK report. c NOEL = no observed effect level: Css exposure (AUC0-166hr µghr/ml/166 hr) for monkeys is the average of males and females.

Genotoxicity

No genotoxicity studies were done: donanemab is not expected to interact with chromosomal material.

Carcinogenicity

No carcinogenicity studies were performed. The company presented a report entitled 'Carcinogenicity assessment for donanemab' and this is summarised below. This concludes that carcinogenic potential of donanemab is low and that carcinogenicity studies in animals are not justified for donanemab.

The company considered the findings from general toxicity studies in monkeys given donanemab and in aged PDAPP mice dosed with the murine antibody mE8c, its own clinical trial experience and also published literature on amyloid plaques. Table 12 summarises the studies in animals that relate to evaluation of cancer risk and shows there were none found.

Donanemab is made of amino acids and monosaccharides and no cancer risk is identified from this. The company considered also that as the target of donanemab is an epitope found in brain amyloid plaque only, that a standard rodent carcinogenicity bioassay is not relevant as normal animals do not express the antibody target.

In general toxicity studies, changes that might associate with induction of cancer such as chronic inflammation, hormonal perturbations, tissue hyperplasia or immunosuppression were not seen. The company also stated that reports of malignancy in clinical trial subjects do not indicate increased risk, whether dosed with donanemab, or in published studies with patients dosed with other amyloid beta-targeting antibodies.

Mice completely deficient in APP were generated and in reports from the 1990s were noted as appearing normal and healthy up to 6 months of age. In studies in aged PDAPP mice, tumours occurred but with no differences to tumours in study controls.

The company noted that donanemab, like other antibodies targeting amyloid beta proteins (aducanumab, bapineuzumab, gantenerumab) increases amyloid-related imaging abnormalities (ARIA) in patients in clinical trials. The company stated that as chronic dosing in animals does not lead to comparable changes, additional animal studies will not be informative in elucidating consequences of these vascular changes in humans.
Regarding the normal function of amyloid beta, this is not clear, but removal of plaque is not identified as a mechanism likely to elicit cancer. Some evidence indicates that amyloid beta inhibits tumour growth and there is a proposed inverse relationship between Alzheimer's disease and cancer: patients have notably lower rates of cancer than do controls. The basis for this is not known.

Overall, the company considered that there is no increased risk of cancer with donanemab. The company also considered that no further experimental studies in animals were needed to conclude on this issue.

Table 12: Summary of findings pertinent to carcinogenic potential in non-clinical studies conducted with donanemab (LY3002813) or mE8C (LSN3026818).

Study Number	Description	Findings Pertinent to Carcinogenicity Risk
8242713	6-week repeat-dose toxicity + 3-month recovery (primates, 2 to 4 years old) Vehicle control and 3 LY3002813 dose levels. N = 36 (3/sex/group, dosing and recovery phases)	No LY3002813-related mortality, clinical observations, body weight or food consumption effects, clinical pathology findings, or anatomic pathology findings occurred.
504299	6-week repeat-dose toxicity in PDAPP mice (12 to 15 months old at study start) Vehicle control and 3 mE8c dose levels. N = 78 (9 or 10/sex/group)	No mE8c-related mortalities, clinical observations, body weight or food consumption effects, clinical pathology changes, or anatomic pathology changes occurred. Hyperplastic and neoplastic findings in this study were common spontaneous age-related occurrences in mice, distributed evenly across dose groups, exhibited no dose response, and were not mE8c-related. In males, lymphoma was observed in 1 of 10 controls, 2 of 10 low-dose, 2 of 9 mid-dose, and 2 of 10 high-dose mice. In females, lymphoma was observed in 2 of 10 control, 3 of 9 low-dose, 0 of 10 mid-dose, and 0 of 10 high-dose mice. Granulocytic leukemia occurred in 1 control female.
8222-743	6-month repeat-dose toxicity in female PDAPP mice (approximately 16 months old at study start) Vehicle control and 3 mE8c dose levels N = 15 females/group	No mE8c-related mortalities, clinical pathology changes, or anatomic pathology changes occurred. All hyperplastic and neoplastic findings were common spontaneous age-related occurrences in mice and were not mE8c-related. <u>Incidence of neoplasms</u> Lymphoma: 7 of 15 control and 4 of 15 high-dose mice Pulmonary adenocarcinoma: 1 of 15 high-dose mice Pituitary adenoma: 2 of 15 control and 1 of 15 high-dose Pulmonary adenoma: 1 of 15 mice from each group Pheochromocytoma: 1 of 15 high-dose mice
504531	6-month repeat-dose toxicity in aged (12 to 15 months old at study start) PDAPP mice Vehicle control and 2 mE8c dose levels N = 19 or 20/sex/group	No mE8c-related mortalities, clinical signs, body weight or food consumption effects, clinical pathology changes, or anatomic pathology effects were observed. Spontaneous age-related malignant lymphoma was the most common cause of death and reason for preterminal euthanasia. Animals from control and treatment groups were similarly affected and mortality was not related to treatment.
MB135	3-month repeat-dose brain microhemorrhage and neuropathology study in PDAPP mice (23 to 24 months old at study start) Vehicle control, positive control, and 2 mE8c dose levels Group size 15 to 16 males/group; 23 to 27 females/group	Brain-only evaluation: No mE8c-related findings
20008867	Ex vivo tissue cross-reactivity study in a panel of cynomolgus monkey and human tissues	No biologically relevant binding.

Note: test article = donanemab in humans and primates and mE8c in transgenic mice.

The MHRA noted that the association between Alzheimer's disease and cancer is a well-established observation. Mechanistically, amyloid beta could elicit a mitotic stimulus that could lead to proliferation but could lead to death of post-mitotic cells such as neurones. This does not particular suggest a risk of cancer arising from use of donanemab. The MHRA concluded that the company's summary suffices as a suitable review and no risk of cancer is identified with use of this drug.

Reproductive and developmental toxicity

No reproductive or developmental toxicity studies, including in juvenile animals, were done.

The company presented a reproductive safety assessment for donanemab and this is summarised below. In brief, it conclusion is that its risks to reproductive health are low. Reproductive risks for donanemab were considered based on information from tissue cross reactivity and toxicology studies with donanemab and with mE8c in PDAPP transgenic mice and from literature on amyloid plaques and its relationship to developmental and reproductive risk. The company also took note of the age and disease status of the intended patient population.

In tissue cross-reactivity studies in human and monkey tissue, no membranous (i.e. biologically pertinent) binding of donanemab was seen in any tissue, including reproductive tissues.

In general toxicity studies in monkeys given donanemab, there were no histopathological signals of reproductive toxicity in general toxicity studies. These monkeys were aged 2-4 years and likely did not express the target of donanemab.

In studies in aged PDAPP transgenic mice given mE8c (murine surrogate of donanemab) for up to 6 months, no findings in reproductive tissues were identified in sexually mature male or female mice. There was evidence of senescence of the female reproductive tissues such as ovarian atrophy, uterine endometrial hyperplasia and vaginal features typical of decreased oestrous cycling in female mice and testicular histology showed features of normal spermatogenesis, supporting low fertility risk in donanemab-treated men.

Table 13: Summary of findings pertinent to potential for reproductive risk from toxicology studies with donanemab or from hazard identification studies in PDAPP transgenic mice with mE8c.

Study Number	Description	Test Article-Related Findings in Reproductive Tissues
20008867	Evaluation of antibody cross-reactivity in tissues from normal human donors (subjects without AD) and naïve nonhuman primates	No membranous (biologically pertinent) binding in human or monkey reproductive tissues
8242713	6-week repeat-dose toxicity + 3-month recovery (primates, 2 to 4 years old)	no findings
504299	6-week repeat-dose toxicity in PDAPP mice (12 to 15 months old at study start)	no findings
8222-743	6-month repeat-dose toxicity in female PDAPP mice (approximately 16 months old at study start)	no findings
504531	6-month repeat-dose toxicity in aged PDAPP mice (12 to 15 months old at study start)	no findings
MB135	3-month repeat-dose brain microhemorrhage and neuropathology study in PDAPP mice (23 to 24 months old at study start)	Reproductive tissues not assessed microscopically

Abbreviations: AD = Alzheimer's disease.
Source: Table APP.1.1, Table APP.1.2, and Table APP.1.3.
Note: test article = donanemab in humans and primates and mE8c in PDAPP transgenic mice.

Developmental and reproductive toxicology studies in animals were judged not to be of relevance due to the absent nature of the target of donanemab (N3pG-containing amyloid plaque) in younger animals: this is present only in the central nervous system of older animals which are a population with limited fertility. Younger rats, mice, rabbits and primates do not express the pharmacological target.

Based on the known biology and nature of the target, removal of N3pG-containing amyloid plaque by donanemab would not be expected to impact reproductive safety. The intended patient population are elderly and have a life-threatening neurodegenerative condition without existing effective treatment options. The company concluded that potential for benefit outweighs the risk of reproductive toxicity in these patients.

Other toxicity studies

Separate local tolerance studies were not done: relevant endpoints were evaluated in general toxicity studies.

Studies into antigenicity, immunotoxicity, dependence, metabolites and impurities were not done. Potential toxicities of impurities were evaluated as part of the general toxicity study in monkeys. The company considered that the proposed impurity specifications for donanemab drug substance and drug product are supported by these studies. The company made a positive affirmation that no risk of presence of nitrosamines was identified.

Conclusions on toxicology

Donanemab is a humanised immunoglobulin (Ig)G1 antibody directed at an N-terminal pyroglutamate (N3pG) amyloid beta epitope present only in brain amyloid plaques. This target is not expected to be present in normal animals.

In a cross-reactivity study in tissues with each of cynomolgus monkeys and humans, no binding of donanemab was identified except to plaque from brain tissue of patients with Alzheimer's disease. No specific binding to membranal targets was identified in either humans or monkeys. The target antigen (N3pE peptide) is extracellular and is not bound to cells. This profile indicates that donanemab is not likely to cause antibody-dependent cell mediated cytotoxicity or complement dependent cytotoxicity.

Cynomolgus monkeys can be considered to be non-pharmacologically responsive to donanemab as they lack the target antigen: studies in such animals address potential for off-target effects. The longest duration of study in monkeys was 6 weeks: normally a longer study (e.g. over 6 months) is required but where the antigen is not present, and testing over a short period does not identify effects of potential concern, it does not make sense to test in monkeys over a longer period. Longer term studies would not be expected to indicate anything of relevance to the human population who will be exposed to this drug. With weekly dosing at up to 100 mg/kg there was little or no accumulation of donanemab: exposure increased in approximate proportion with an increase in dose. No differences were noted in exposure parameters between male and female monkeys.

No toxicity was identified in the general toxicity study in cynomolgus monkeys where the drug was given up to 100 mg/kg intravenously once weekly over 6 weeks. In monkeys, there were no effects noted on safety pharmacology measures (effects on vital system) and the drug was judged well tolerated at injection sites.

In contrast, PDAPP mice express amyloid beta and develop plaques in which the target epitope is present. They can be considered as pharmacologically relevant and the company presented general toxicity studies in these mice. However, use of the humanised antibody donanemab, would likely be immunogenic and so such studies were done with murine antibody, mE8c (anti amyloid beta p3-x, IgG2a), which targets the same antigen; studies were also done with mE8 (anti-amyloid beta p3-x, IgG1), which lacks effector function. Studies in PDAPP transgenic mice are considered relevant to identify possible on-target effects; however, of note, was that the duration of dosing in PDAPP transgenic mice was limited by the normal lifespan of these mice; to ensure presence of amyloid plaque, studies were initiated in elderly mice, aged at least 12 months old. Exposure to antibody was shown to be sustained in these studies and increased with the dose.

Across several studies, no toxicity was identified in PDAPP mice given either m8Ec or m8E, antibodies that, respectively have and do not have, effector function (donanemab does have effector function, necessary for its action via phagocytosis). Doses were given up to 100 mg/kg and over 6 months. Although there were a number of unscheduled deaths, this was expected in studies starting in such aged mice and there was no pattern of excess death in mice given mE8 or mE8c, as compared controls.

Studies in monkeys and mice included an expanded neuropathologic evaluation of the brain. Evaluation of a risk of bleeding in the brain was undertaken. There may be a role for the presence of amyloid to weaken blood vessels, so promoting a risk of cerebral haemorrhage. Patients with Alzheimer's disease do have an increased risk of cerebral haemorrhage: use of antibody may increase the risk further in patients. The company tried to replicate this in studies in PDAPP mice expressing amyloid beta but no effect was seen to exacerbate bleeding the brain with surrogate antibodies, mE8 and mE8c. This was despite there being such an effect with a positive control antibody, 3D6.

The company did not conduct studies into genotoxicity or carcinogenicity. There is no expectation that an antibody will cause genotoxicity. The company presented a detailed review of the risk of cancer with its antibody which concluded that there is no particular evidence supporting a concern. The product is initiated in elderly patients and although its duration of use is not limited, treatment is indicated until plaques are cleared; treatment can be continued for up to 18 months where plaque monitoring is not available. Thus, use over a much longer period than this is not anticipated for most patients.

Given the age of patients likely to be treated, no reproductive toxicity studies in animals were done. The SmPC does not specify a minimum age but the clinical trial experience was mostly in patients over 60 years old. For this population, both age and their condition make it likely that reproductive toxicity is of no concern and the absence of studies can be accepted.

Overall, the toxicity data suffice to characterise this drug: no further studies are needed.

III.5 Ecotoxicity/Environmental Risk Assessment

An Environmental Risk Assessment (ERA) was submitted with this application. The company summarised that this product does not contain genetically modified organisms.

As a monoclonal antibody, it is expected to be metabolised in the administered patient to smaller peptides and its constituent amino acids. It is not expected to persist in the environment. The use of donanemab in humans is not expected to result in a significant risk to the environment.

The effects of the finished product on the environment have been fully characterised, in line with current guidance. No further action regarding the environmental fate of this product is required.

III.6 Discussion on the non-clinical aspects

The non-clinical aspects are discussed in summaries at the end of the pharmacology, pharmacokinetics and toxicology sections. The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical efficacy data to support slowing of disease progression were based on the results of the Phase 3 confirmatory study, AACI, of which the placebo-controlled primary outcome study period has completed (AACI-PC), with supportive evidence based on the Phase 2 Study AACG. Other studies supporting biomarker assessments included 6-month efficacy data from the ongoing active comparator Phase 3 Study AACN, and to help determine dosing included in the Phase 1 Studies AACC and AACD.

Two studies were ongoing: AACH trailblazer Ext. for participants who completed AACG on placebo will provide data up to 48 weeks of donanemab exposure to assess safety outcome (IDB only), clinical efficacy assessment and clinical pharmacology biomarker data remain pending until completion. The other ongoing study was a Phase 3 comparing amyloid plaques removal effectiveness of donanemab vs aducanumab (not approved in EU or UK but only US).

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

Table 14: Listing of Donanemab clinical studies to support registration.

Identifier and Description	Cohort, *status*	Role in Labelling
AACI (TRAILBLAZER-ALZ2) Multicentre, randomised, double-blind, placebo-controlled, Phase 3 study of donanemab in participants with early symptomatic AD with the presence of brain amyloid and low-medium or high tau levels	AACI-PC, *completed*	Placebo-controlled primary outcome cohort with a 76-week DB period, contributing up to 72 weeks of study treatment, to assess clinical pharmacology, efficacy, and safety outcomes.
	AACI-LTE, *ongoing*	Long-term safety extension for participants who completed the PC period, contributing up to 72 weeks of donanemab exposure, to assess safety outcomes (IDB only). The efficacy and clinical pharmacology biomarker data remain blinded.
	AACI-Safety Addendum, *ongoing*	Direct enrolment, open-label addendum, contributing up to 72 weeks of donanemab treatment, to assess safety outcomes (IDB only). The clinical pharmacology biomarker data remain pending until study completion. The addendum does not include any efficacy assessment.
AACG (TRAILBLAZER-ALZ) Multicentre, randomised, double-blind, placebo-controlled, Phase 2 study of donanemab in participants with early symptomatic AD and low-medium tau levels	*Completed*	Placebo-controlled study with a 76-week DB period, contributing up to 72 weeks of study treatment, to assess clinical pharmacology, efficacy, and safety outcomes.
AACH (TRAILBLAZER-EXT) Phase 2, open-label extension study in patients with symptomatic AD who participated in a DB treatment period of a sponsor-approved originating donanemab trial (Study AACG or AACC). Part B is a multicentre, open-label study of donanemab for participants who received placebo in originating Study AACG	Part B, *Ongoing*	Open-label extension for participants who completed Study AACG on placebo, contributing up to 48 weeks of donanemab exposure, to assess safety outcomes (IDB only). Clinical efficacy assessments and clinical pharmacology biomarker data remain pending until study completion.
AACN (TRAILBLAZER-ALZ4) Open-label, parallel-group, 2-arm, Phase 3 study comparing amyloid plaque clearance with donanemab compared with aducanumab in participants with early symptomatic AD	Dona treatment group, *Ongoing*	Active comparator study with a 76-week, open-label study period, contributing clinical pharmacology biomarker data and safety data up to 72 weeks of donanemab treatment, to assess biomarker and safety outcomes. No clinical efficacy assessment was conducted. Participants randomly assigned to donanemab were included in the IDB.

Abbreviations: AD = Alzheimer's disease; DB = double-blind; Dona = donanemab; IDB = integrated database; LTE = long-term extension; PC = placebo-controlled.

IV. 2 Pharmacokinetics

Introduction

The clinical pharmacology program for donanemab had the following goals:

- to characterise the safety, PK and PD profile of donanemab, and
- to identify safe and effective dosing regimens for donanemab efficacy studies and commercialisation

A list of the studies carried out is given below. Also, population PK/PD analyses and immunogenicity analyses were performed.

- Studies AACC and AACD were conducted in patients with mild cognitive impairment due to AD or mild-to-moderate AD.
- Studies AACG and AACI were conducted in patients with early symptomatic AD.
- Study AACH was conducted in patients with symptomatic AD with validation of remote neurophysiological assessments.

Study	Phase	Study Aim
AACC	1	To assess the safety, tolerability, and PK profile of single and multiple IV doses of donanemab
AACD	1b	To assess the safety, tolerability, PK, and PD profiles of single and multiple IV doses of donanemab
AACG	2	To evaluate the safety and efficacy of donanemab and assess whether removal of existing amyloid plaque can slow progression of AD in up to 72 weeks of treatment
AACH (Part B) (Part C)	2	Part B: To evaluate the safety and tolerability of donanemab; to assess the effect of donanemab on clinical progression, brain amyloid deposition, and brain region volumes; and to assess the peripheral PK and presence of anti-donanemab antibodies Part C: To assess the long-term effect of donanemab on PET imaging biomarkers, cognition, and function in participants who have not received donanemab for at least 52 weeks
AACI-PC	3	To assess the effect of donanemab on clinical progression of AD, brain amyloid deposition, brain tau deposition, and brain region volumes; to evaluate the safety and tolerability of donanemab; and to assess the peripheral PK and presence of anti-donanemab antibodies
AACI-Safety Addendum	3	To evaluate the safety and tolerability of donanemab; to assess the peripheral PK and presence of anti-donanemab antibodies; and to assess the effect of donanemab on brain amyloid deposition and blood-based biomarkers

Abbreviations: AD = Alzheimer's disease; IV = intravenous; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Table 15: Studies included for each endpoint analysis.

Endpoints	PK Analysis	Amyloid PET	ARIA-E	Plasma P-tau217	Plasma GFAP	iADRS and CDR-SB
Studies Included	AACD, AACG, AACI (PC, Safety Addendum), AACH, Part B	AACD, AACG, AACI (PC), AACH, Part C	AACG, AACI (PC, Safety Addendum)	AACI (PC)	AACG, AACI (PC)	AACG, AACI (PC)

Abbreviations: ARIA-E = amyloid-related imaging abnormalities–oedema/effusions; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; GFAP = glial fibrillary acidic protein; iADRS = integrated Alzheimer's Disease Rating Scale; PET = positron emission tomography; PK = pharmacokinetic.

Four formulations supported clinical development, including the solution formulation, which is the final commercial formulation. Doses from 0.1 to 40 mg/kg, as well as 700 to 1400 mg, have been explored across the clinical studies.

Table 16: Summary of drug product and container closure system for use in clinical studies.

Formulation Used	Study Identifier
Lyophilized in a 5-mL vial (40 mg)	I5T-MC-AACC
Lyophilized in a 5-mL vial (120 mg)	I5T-MC-AACD
Lyophilized in a 50-mL vial (700 mg)	I5T-MC-AACG I5T-MC-AACI
Solution in a 20-mL vial (350 mg)	I5T-MC-AACH I5T-MC-AACI I5T-MC-AACN

Both lyophilised and solution formulations of donanemab have largely been administered IV. A pilot evaluation of BA following SC administration was conducted as part of the initial clinical study AACC. Due to the relative high doses required for efficacy, donanemab was administered IV in the Phase 2 and 3 studies.

Analytical Methods – PK analytical methodology for studies AACC and AACD
The ELISA methods were developed and validated for the quantification of donanemab concentrations in human serum and human CSF. Serum samples collected at baseline and after dosing in clinical studies were analysed for donanemab using a validated ELISA. Details of the method and history of the assay performance for assessing donanemab serum concentrations were provided including validation range, interassay precision, interassay accuracy, dilutional linearity, and stability of donanemab. Quality control samples across the standard curve range were included in each sample analysis batch.

An antigen-capture ELISA method was developed and validated to quantify donanemab in human serum and in human CSF. An antibody-drug-antibody (ADA) assay was also developed. The assay performance met validation criteria for precision, accuracy, dilutional linearity, selectivity, and stability. Matrix has been evaluated using serum from AD patients and no major concerns have been identified. The applicant provided information and certificates of analyses where required for all the critical reagents required for the assay.

Validations and cross-validation experiments were performed to bridge across the major method revisions. For minor changes, standard curve and quality control performance were evaluated, and the continued performance of the assay was demonstrated as robust in study assay acceptance rate and successful incurred sample analysis.

Study I5T-MC-AACC

This study was a single-dose and multiple-dose, dose-escalation study to evaluate the safety, tolerability, and PK of LY3002813 in patients with mild cognitive impairment (MCI) due to AD or mild-to-moderate AD.

Objectives:
The primary objective was to explore the safety and tolerability features of single and multiple doses of donanemab in Japanese and non-Japanese patients with MCI due to AD or mild-to-moderate AD, to define an appropriate dose range for further clinical research.

Secondary objectives were to assess the serum PK of IV and SC single dose and IV multiple doses of donanemab in Japanese and non-Japanese patients with MCI due to AD or mild-to-moderate AD, and to assess the effect of donanemab on amyloid plaque using florbetapir imaging.

The exploratory objectives relevant to pharmacokinetics and pharmacodynamics were:

- To assess the serum PK of a single IV dose of donanemab in young, healthy, male participants
- To evaluate changes in plasma, serum, and CSF biomarkers following multiple doses of donanemab
- To measure CSF donanemab levels after multiple doses of donanemab via IV

Study Design and Methodology

This single and multiple dose, placebo-controlled, dose-escalation study was the first assessment of the safety, tolerability and PK of a wide range of donanemab.

The PK of donanemab was assessed after a single dose in the SAD phase, and after every dose in the MAD phase, with further samples taken up to approximately 12 weeks after the final dose. Florbetapir scans were performed at screening and after the last MAD dose, separated by up to approximately 7 months, to assess the PD effects of donanemab on amyloid plaque. Serial MRIs were performed for assessment of amyloid-related imaging abnormalities (ARIA-E and ARIA-H).

Results

In the SAD phase, the Cmax values of donanemab across the dose groups were dose proportional. After single-dose administration from 0.1 to 3 mg/kg, the mean terminal elimination half-life was approximately 4 days, increasing to approximately 10 days at the 10 mg/kg dose level.

Table 17: Noncompartmental pharmacokinetic parameters following a single dose of donanemab in participants with mild cognitive impairment due to Alzheimer's disease or mild-to-moderate Alzheimer's disease – Study AACC.

	Geometric Mean (CV%)						
Treatment	**0.1 mg/kg IV**	**0.3 mg/kg IV**	**1 mg/kg IV**	**1 mg/kg IV HV**	**3 mg/kg IV**	**3 mg/kg SC**	**10 mg/kg IV**
N	**4**	**7**	**9**	**6**	**11**	**8**	**6**
C_{max} (µg/mL)	2.90 (35%)	5.99 (77%)	21.7 (21%)	31.5 (29%)	71.6 (24%)	12.0 (34%)	218 (16%)
t_{max}[a] (h) (range)	1.75 (0.50-24.00)	0.50 (0.50-72.00)	0.50 (0.50-3.27)	0.50 (0.50-3.00)	0.50 (0.50-24.80)	120.0 (70.1-336.0)	3.00 (0.50-3.00)
$t_{1/2}$ (day)	2.26 (37%)	4.64 (63%)	4.84 (58%)	3.19 (24%)	5.40 (55%)	7.47 (40%)	10.5 (50%)
AUC(0-t_{last}) (µg•day/mL)	6.78 (31%)	23.7 (36%)	78.4 (26%)	90.8 (17%)	261 (19%)	152 (44%)	1130 (40%)
AUC(0-∞) (µg•day/mL)	7.94 (32%)	26.3 (33%)	79.9 (26%)	91.6 (17%)	263 (19%)	157 (41%)	1140 (39%)
AUC(t_{last}-∞) (%)	13 (62%)	7 (100%)	2 (30%)	1 (31%)	1 (89%)	2 (156%)	0 (245%)
CL[b] (L/h)	0.0310 (37%)	0.0305 (34%)	0.0321 (32%)	0.0355 (27%)	0.0318 (33%)	0.0269 (58%)	0.0260 (25%)
V_z[b] (L)	2.42 (59%)	4.89 (69%)	5.39 (56%)	3.92 (32%)	5.95 (60%)	6.96 (56%)	9.41 (44%)

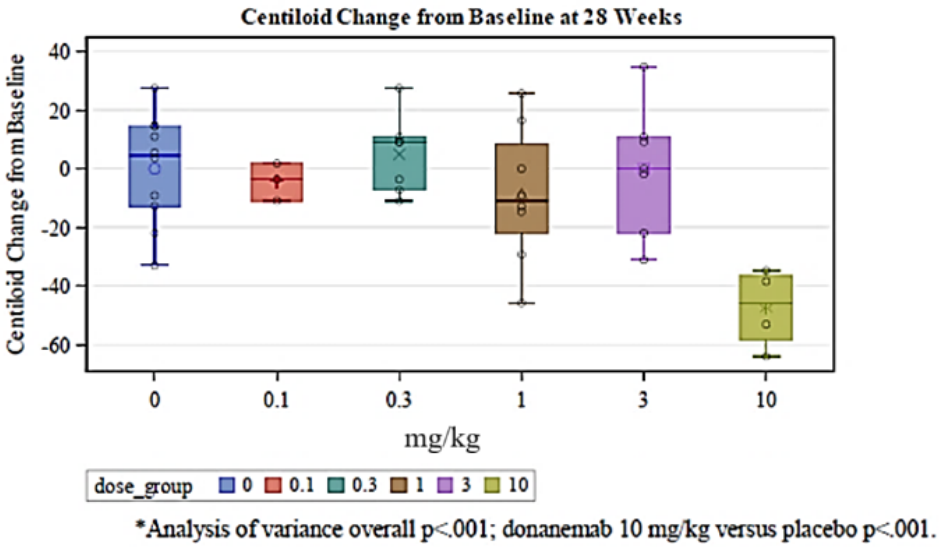
In the MAD phase, most participants at dose levels ≤ 3 mg/kg had serum donanemab concentrations below the limits of detection 28 days after dosing. For the dose groups ≤ 3 mg/kg serum concentrations following multiple doses of donanemab were lower than those observed after the first dose.

This may be attributed to the development of treatment-emergent (TE) antidrug antibodies (ADA), which were found to increase over time during the MAD dosing period. For the 10 mg/kg dose group, serum concentrations were similar following first and multiple doses of donanemab.

The CSF samples collected in the study show that donanemab was able to reach the CNS in participants treated with 1, 3 and 10 mg/kg doses. The ratio of CSF to serum concentrations of donanemab (0.171%) is consistent with other monoclonal antibodies.

Analysis of the florbetapir PET scans were performed according to a SUVr method. The latter SUVr values were converted to Centiloid units. Comparison of images at baseline (visit 3, 2 weeks before the first dose) and 28 weeks after first dose (Visit 18) is shown in the following figure using Centiloid units.

Figure 18: Change in florbetapir Centiloid units from baseline at 28 weeks for donanemab – study AACC.



*Analysis of variance overall p<.001; donanemab 10 mg/kg versus placebo p<.001.

There was a statistically significant change in florbetapir Centiloid units from baseline at 28 weeks at the highest donanemab dose of 10 mg/kg ($p<0.001$).

Study I5T-MC-AACD

Study I5T-MC-AACD (AACD) was a 3-part, patient- and investigator-blind, randomised within cohort, placebo-controlled, parallel-group, single- and multiple-dose study in participants with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or mild to moderate AD to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple intravenous (IV) doses of LY3002813

Objectives:
The primary objective was to assess the effect of donanemab on amyloid plaque level using florbetapir PET imaging in Japanese and non-Japanese participants with MCI due to AD or mild-to-moderate AD.

The secondary objectives were:

- to evaluate the safety and PK of single and multiple doses of donanemab in Japanese and non-Japanese participants with MCI due to AD or mild-to-moderate AD
- to evaluate the immunogenicity of single and multiple doses of donanemab.

Methods:
Study AACD was a Phase Ib study to assess the safety, tolerability, PK and PD of single and IV doses of donanemab. This was a multicenter, participant and investigator blind, randomised within cohort, placebo controlled, parallel group, single and multiple dose study.

For single dose cohorts, the PK of donanemab was assessed regularly post-dose. For multiple-dose cohorts, PL was assessed after the first dose and then samples were taken regularly during the dosing period, including end of infusion and trough concentrations. Florbetapir scans were performed at screening, baseline and then at 12, 24, 36, 48 and 72 weeks after starting treatment. Serial MRIs were performed for assessment of ARIA-E and ARIA-H

Dosing of Study AACD was conducted in 3 parts (A, B and C, see Table 18). Doses of 10, 20 and 40 mg/kg donanemab were administered IV as follows.

Table 18: Dosing in Study AACD.

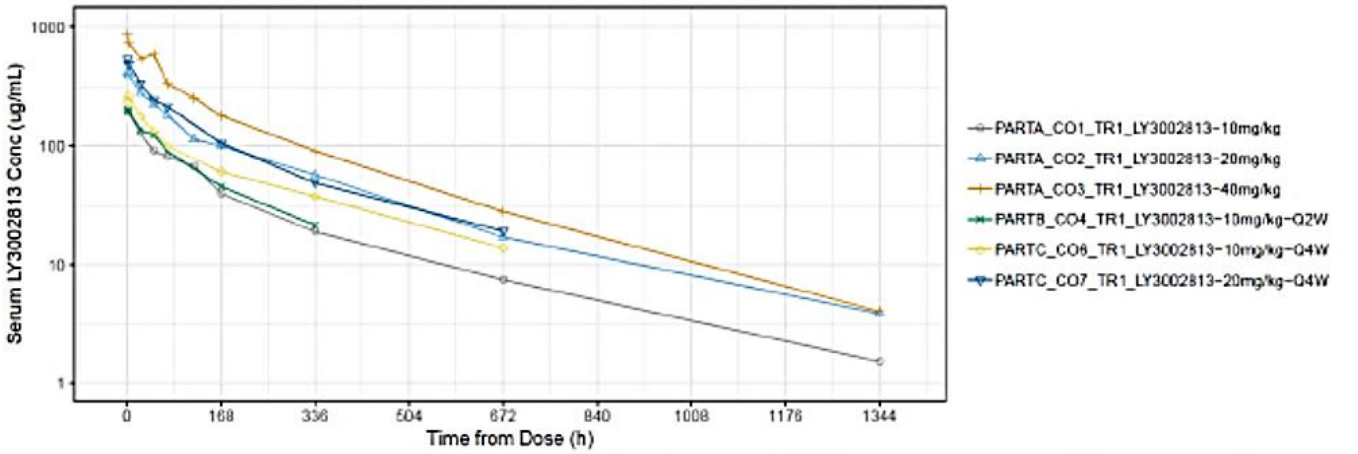
Dose Level	Part A Single Dose	Part B Multiple Dose (Q2W for 24 weeks)	Part C Multiple Dose (Q4W for 72 weeks)
10 mg/kg	Cohort 1	Cohort 4	Cohort 6
20 mg/kg	Cohort 2	Cohort 5	Cohort 7
40 mg/kg	Cohort 3		

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks.

Single dose results
Donanemab concentrations increased linearly with increase in dose in a dose-proportional manner (dose range 10 to 40 mg/kg). Observed CSF to serum concentration ratio was approximately 0.208% across all participants and dose levels.

Results following single doses of donanemab 10, 20, and 40 mg/kg in Cohorts 1, 2 and 3 showed a mean elimination half-life of 10.3, 9.3 and 8.3 days, respectively. The geometric mean clearance was similar across the single-dose cohorts (approximately 0.022 to 0.026 L/h).

Figure 19: Mean serum concentration versus time profiles, on semi-logarithmic plot, following single doses of donanemab 10, 20 and 40 mg/kg in Cohorts 1, 2 and 3 respectively; and first dose administration of donanemab 10 mg/kg Q2W, 10 mg/kg Q4W, and 20 mg/kg Q4W in Cohorts 4, 6 and 7 respectively – Study AACD.



Abbreviations: Conc = concentration; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: Data points were plotted only if 2/3 or more of the individual data from the same cohort at each time point were quantifiable.

Table 19: Summary PK parameters for Cohorts 1, 2 and 3 following single-dose administration of donanemab – Study AACD.

Geometric Mean (CV%) Serum Donanemab			
Treatment	**Donanemab 10 mg/kg**	**Donanemab 20 mg/kg**	**Donanemab 40 mg/kg**
Cohort	1	2	3
Na	7/7	7/7	4/4
C_{max} (ug/mL)	196 (17)	413 (17)	910 (15)
t_{max}[b] (h)	2.07 (1.28-3.20)	2.07 (1.78-3.02)	2.90 (2.47-3.22)
$t_{1/2}$[c] (days)	10.3 (5.4-14.5)	9.3 (5.6-16.2)	8.3 (6.8-11.3)
CL (L/h)	0.0264 (45)	0.0238 (15)	0.0221 (14)
V_Z (L)	9.40 (57)	7.70 (46)	6.36 (23)
$AUC_{(0\text{-tlast})}$ (µg·h/mL)	25700 (20)	59400 (19)	110000 (32)
$AUC_{(0\text{-}\infty)}$ (µg·h/mL)	26200 (19)	60500 (18)	112000 (30)

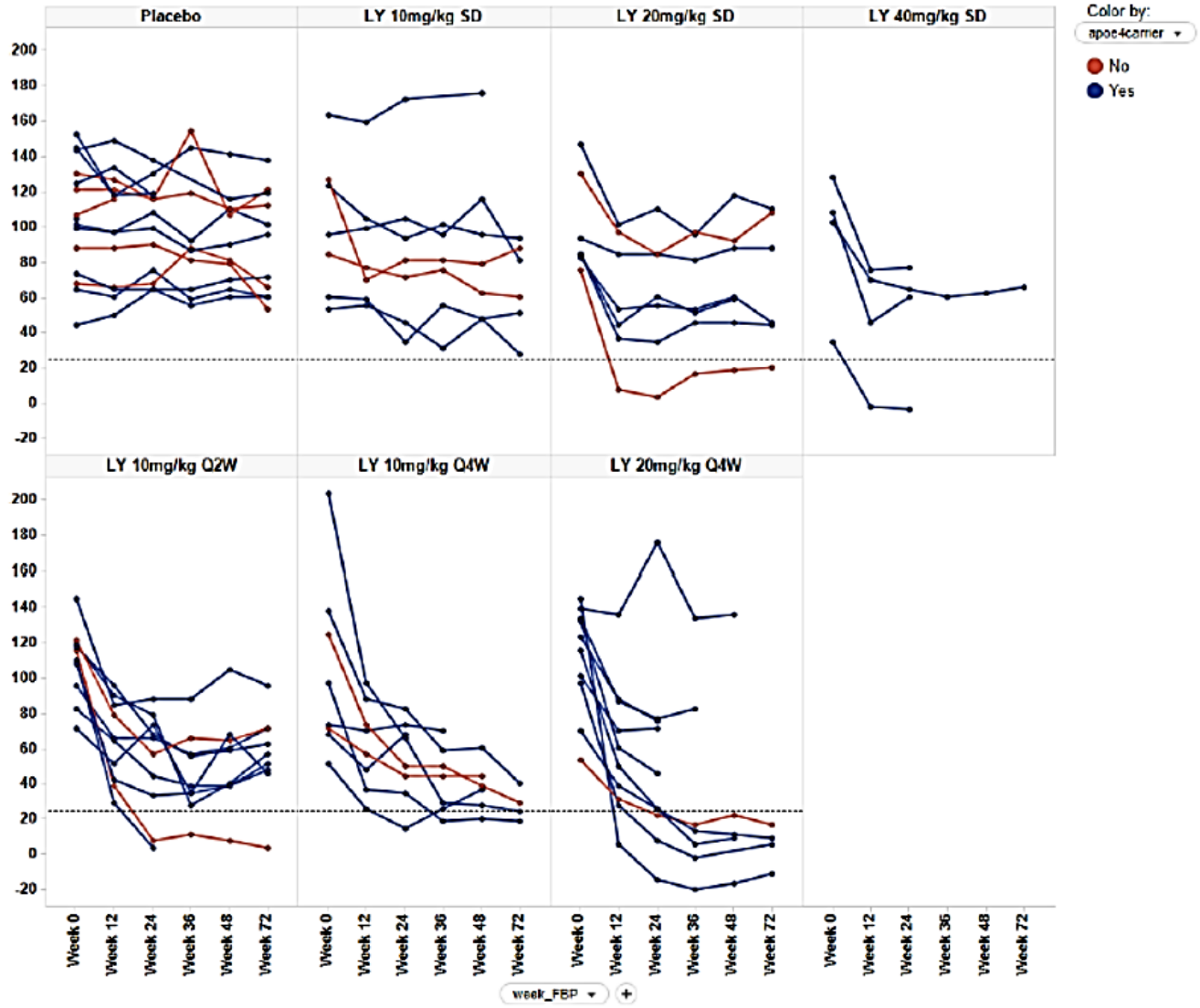
Multiple dose results

At steady state on Day 127 and Day 141, the median time of Cmax at steady state (infusion end) ranged from 1.38 to 2.23 hours post dose, independent of dose. Both Cmax,ss and exposure increased with dose. The geometric mean CLss was similar across cohorts (approximately 0.02 L/h). No accumulation of donanemab was observed with the 10 mg/kg Q4W, as shown by the accumulation ratio (RA approximately 1). There was limited accumulation with donanemab 10 mg/kg Q2W and 20 mg/kg Q4W with RA of 1.29 and 1.26, respectively. Additionally, the Cmax and AUC0-t on Day 1 and at steady state (Day 127/141) in the same participant, following 10 or 20 mg/kg Q4W dosing, appeared to be similar.

PD results

A statistically significant reduction in amyloid plaque level, as measured using florbetapir PET was observed across most dosing regiments in a dose-dependent manner.

Figure 20: Individual change over time (in weeks) in amyloid plaque as measured by florbetapir PET (in Centiloids) per visit per treatment – study AACD.



Abbreviations: APOE= apolipoprotein E; FBP = florbetapir; LY = donanemab; PET = positron emission tomography; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = single dose.
Note: Color by APOE ε4 carrier status: Red for No, Blue for Yes. The black dashed horizontal line (24.1 Centiloid) indicates threshold Centiloid value for being amyloid positive. Note that the Q2W dosing regimen was continued for only 24 weeks.

ARIA-E safety results

In study AACC, no ARIA-Es were observed up to 10 mg/kg.

In study AACD, amyloid-related imaging abnormalities-edema/effusions (ARIA-E) was observed in all cohorts, aside from the 10 mg/kg single-dose cohort. All ARIA-E occurrences resolved and were generally considered manageable. The incidence of ARIA-E was highest following single doses of 40 mg/kg donanemab. The incidence observed in the 20 mg/kg dose level was approximately 30%.

Pharmacokinetic data analysis

PK conclusions are based on the population PK (popPK) analysis, which includes data from studies AACD, AACG, AACH parts B and C, AACI-PC and AACI-safety addendum.

Comparison of PK in Healthy Participants and Patients with AD

The potential for differences in PK between young, healthy participants and patients with amyloid plaques was explored in study AACC at a dose level of 1 mg/kg. After a single dose of 1 mg/kg donanemab, PK parameters were generally comparable between healthy study participants and those with AD following the administration of a single dose of 1 mg/kg donanemab.

Table 20: Pharmacokinetics of donanemab in young, healthy participants and participants with Alzheimer's disease following a single intravenous dose of 1mg/kg – Study AACC.

	Geometric Mean (CV%)	
	Healthy Participants	Participants with Alzheimer's Disease
N	6	9
C_{max}	31.5	21.7
(µg/mL)	(29%)	(21%)
t_{max}[a] (h)	0.50	0.50
(range)	(0.50 – 3.00)	(0.50 – 3.27)
$t_{1/2}$ (day)	3.19	4.84
	(24%)	(58%)
AUC(0-t_{last})	90.8	78.4
(µg•day/mL)	(17%)	(26%)
AUC(0-∞)	91.6	79.9
(µg•day/mL)	(17%)	(26%)
CL	0.0355	0.0321
(L/h)	(27%)	(32%)
Vz	3.92	5.39
(L)	(32%)	(56%)

Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; AUC(0-∞) = area under the concentration versus time curve from zero to infinity; CL = total body clearance of drug calculated after intravenous administration; C_{max} = maximum observed drug concentration; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of patients; t_{max} = time of maximum observed drug concentration; $t_{1/2}$ = half-life associated with the terminal rate constant in noncompartmental analysis; Vz = volume of distribution during the terminal phase after intravenous administration.

[a] Median (Min – Max).

Absorption

Donanemab is administered IV and Cmax is achieved at the end of infusion. In a pilot evaluation of SC bioavailability (study AACC), at a dose of 3 mg/kg, BA was approximately 60% and T_{max} occurred approximately 5 days after administration of a single dose of SC 3 mg/kg donanemab. It is unknown whether a similar BA would be observed at higher dose levels.

Distribution

Following IV administration, donanemab PK follows a biphasic profile, consistent with two-compartment PK. Based on the popPK analysis, central volume of distribution is 3.36 L with 18.7% interindividual variability, while peripheral volume of distribution is 4.83 L with 93.9% interindividual variability. In the Phase 1 studies AACC and AACD, the ratio of CSF to serum concentrations of donanemab was approximately 0.2% which is consistent with other mAbs.

Elimination

Donanemab is a mAb and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous IgG. Hence, there is no active metabolite formation or metabolic inhibition or induction of enzymatic pathways. It is also not expected to be metabolised by the CYP450 families of drug-metabolising enzymes responsible for metabolism and elimination of small molecules and would, therefore, not cause CYP450-mediated clinical drug-drug interactions (DDIs) as a victim drug.

Based on popPK analysis, clearance is 0.0255 l/h with 24.9% between-participant variability. Half-life is approximately 12.1 days for a typical participant with weight of 72 kg and maximum ADA titre of 1:2560.

Dose proportionality and time dependency

In doses from 10 mg/kg to 40 mg/kg, AUCinf and Cmax were approximately dose proportional to following single doses. At doses of 10 mg/kg and 20 mg/kg, AUCτ,ss and Cmax,ss were approximately dose proportional at steady state.

Table 21: Summary PK parameters for cohorts 1, 2 and 3 following single-dose administration of donanemab – Study AACD.

Geometric Mean (CV%) Serum Donanemab			
Treatment	**Donanemab 10 mg/kg**	**Donanemab 20 mg/kg**	**Donanemab 40 mg/kg**
Cohort	1	2	3
N[a]	7/7	7/7	4/4
C_{max} (ug/mL)	196 (17)	413 (17)	910 (15)
t_{max}[b] (h)	2.07 (1.28-3.20)	2.07 (1.78-3.02)	2.90 (2.47-3.22)
$t_{1/2}$[c] (days)	10.3 (5.4-14.5)	9.3 (5.6-16.2)	8.3 (6.8-11.3)
CL (L/h)	0.0264 (45)	0.0238 (15)	0.0221 (14)
V_z (L)	9.40 (57)	7.70 (46)	6.36 (23)
$AUC_{(0\text{-tlast})}$ (µg·h/mL)	25700 (20)	59400 (19)	110000 (32)
$AUC_{(0\text{-}\infty)}$ (µg·h/mL)	26200 (19)	60500 (18)	112000 (30)

The PK of donanemab appears to be time linear at the 10- to 20- mg/kg dose levels. No accumulation of donanemab was observed with the 10 mg/kg Q4W dose, as shown by the accumulation ratio (RA) of approximately 1. There was limited accumulation with donanemab 20 mg/kg Q4W with a mean RA of 1.26. The Cmax and AUCτ at Day 1 and at steady state (Days 127 and 141) in the same participant, following 10- or 20 mg/kg Q4W regimens, in general, appeared to be similar.

In doses from 10 mg/kg to 40 mg/kg, AUCinf and Cmax were dose proportional to following single doses.

Pharmacokinetics in target population

The objectives of the popPK/PD analysis were to:

- Characterise the PK donanemab in patients with early symptomatic Alzheimer's disease (AD)
- Identify patient and other factors that impact the PK of donanemab
- Characterise the dose-/exposure-response relationships that describe:
    - Biomarkers (amyloid plaque reduction as measured by PET tracer, reduction in tau pathology as measured by plasma tau phosphorylated at threonine 1217 (P-tau217), and reduction in neuro-inflammation as measured by plasma glial fibrillary acidic protein (GFAP) as marker for astrocytic activation or proliferation)
    - Efficacy (integrated AD rating scale (iADRS)/clinical dementia rating scale – sum of boxes (CDR-SB)
    - Safety (amyloid-related imaging abnormalities-edema/effusion (ARIA-E)) endpoints
- Identify potential factors that may impact the dose-/exposure-response relationship
    - Baseline disease state and tau population impact on clinical efficacy, and
    - Donanemab dose cessation at 6 and 12 months and impact on clinical efficacy
- Explore potential covariates, such as demographic factors, laboratory parameters, immunogenicity, baseline tau burden, baseline amyloid PET, prior and concomitant therapies, and disease characteristic that may influence donanemab disposition in this patient population
- Generate model-predicted estimates of donanemab exposure to support subsequent efficacy and safety analysis, and
- Explore clinical application of any findings above through simulations

Table 22: Data used in the analysis.

Study	Indication/Population	Doses Utilized	N
Study I5T-MC-AACD	Mild cognitive impairment or mild to moderate AD	• Placebo • 10-, 20-, 40-mg/kg single dose • 10 mg/kg Q2W[a] • 10, 20 mg/kg Q4W	61 total (15 placebo, 46 donanemab)
Study I5T-MC-AACG (AACG)	Early symptomatic AD	• Placebo • 700 mg Q4W (3 doses) followed by 1400 mg Q4W	256 total[b] (125 placebo, 131 donanemab monotherapy)
Study I5T-MC-AACH (Parts B and C) (AACH)	Symptomatic AD	Part B: Participants who received placebo in the originating trial receive donanemab 700 mg IV Q4W for 3 doses, then 1400 mg IV Q4W[c] Part C: Single imaging and cognitive/functional assessment visit at least 52 weeks from last double-blind visit in originating study	Part B: 54 Part C: 18
Study I5T-MC-AACI-PC (AACI-PC)	Early symptomatic AD	• Placebo • 700 mg IV Q4W (3 doses), followed by 1400 mg Q4W[c]	1726 total (873 placebo, 853 donanemab)
Study I5T-MC-AACI (Safety Addendum)	Early symptomatic AD	• 700 mg IV Q4W (3 doses), followed by 1400 mg Q4W[c]	1047 total

Abbreviations: AD = Alzheimer's disease; IV = intravenous; N = number of participants represented in the dataset; PC = placebo-controlled; PET = positron emission tomography; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks.

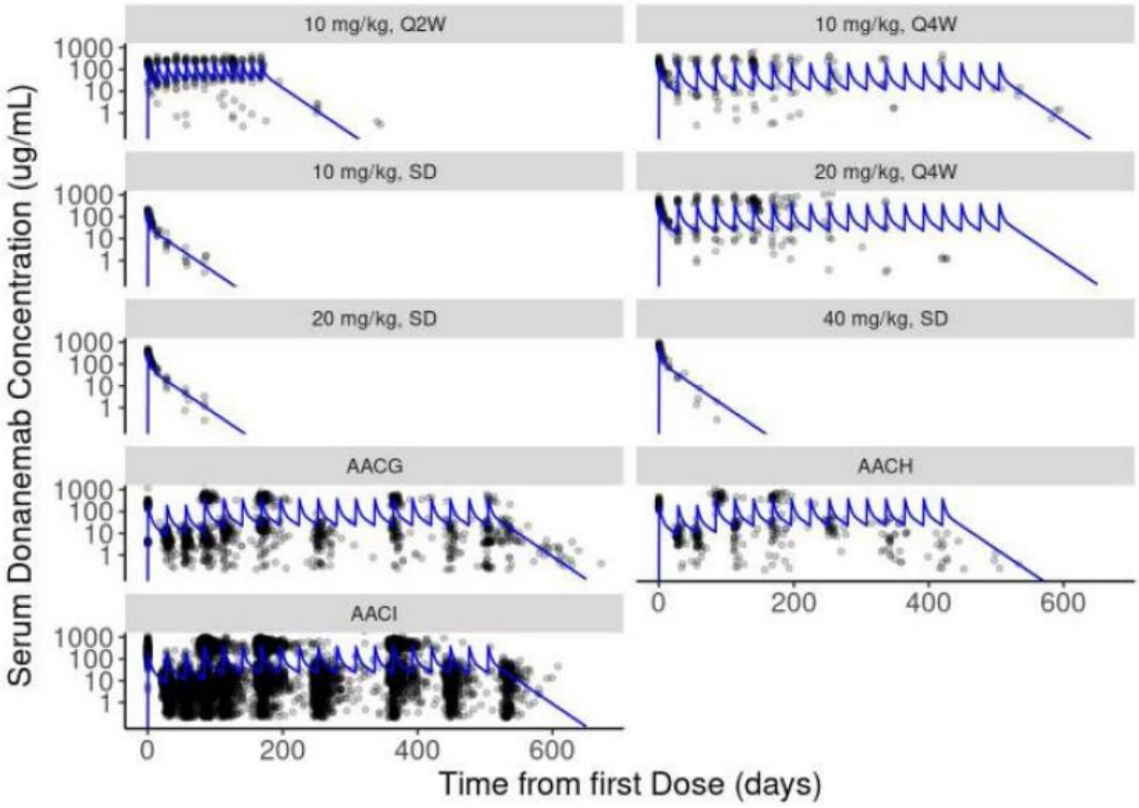
[a] A 20-mg/kg Q2W dose level was planned but was not initiated in Study AACD.

[b] A total of 272 participants were randomly assigned into the study, with 15 participants randomly assigned to the donanemab/LY3202626 combination arm (donanemab-C) prior to amendment of the study to discontinue that arm. These 15 subjects were not included in any of the analyses described in this report. One participant was randomly assigned to placebo but discontinued from the study before receiving an infusion.

[c] Dosing for remainder of the study or when participant met the eligibility criteria for completing active treatment, in which participants would switch to placebo (AACG, AACI-PC) or discontinue donanemab (AACI-Safety Addendum, and AACH). In AACG, participants could also be switched to 700 mg based on amyloid PET.

The observed, quantifiable donanemab concentration-time data included in the analysis are shown below. The PK dataset contained 22,288 observations from 2131 participants.

Figure 21: Observed serum donanemab concentration in Studies AACD, AACG, AACH and AACI.

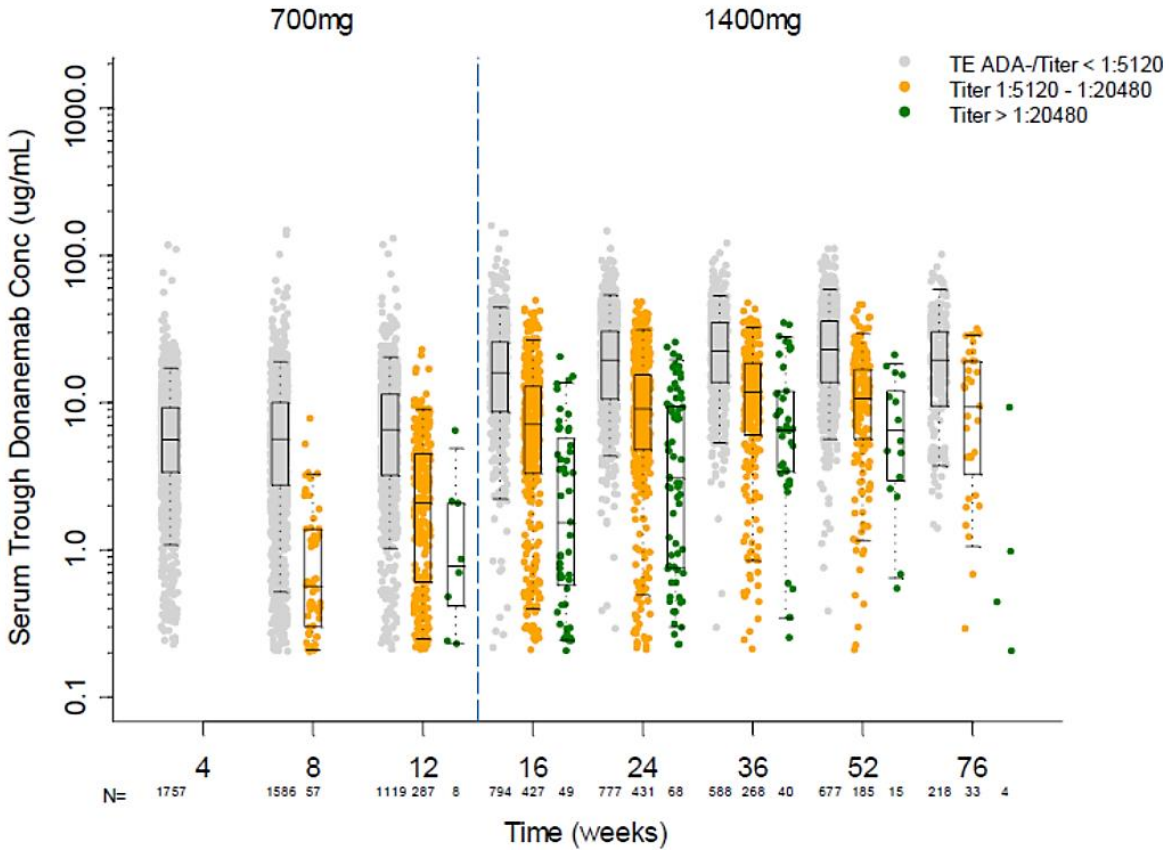


Abbreviations: AACD = I5T-MC-AACD; AACG = Study I5T-MC-AACG; AACH = Study I5T-MC-AACH; AACI = Study I5T-MC-AACI; PK = pharmacokinetics; Q2W = every 2 weeks, Q4W = every 4 weeks; SD = single dose; solid blue line = population prediction from final population model.
Points are observed data used in PK model. The AACG/AACH/AACI titration was 3 doses of 700 mg Q4W, followed by 1400 mg Q4W.

Observed donanemab serum trough concentrations were plotted against ADA titers for studies AACD, AACH, AACI and AACG at different weeks. Although there is variability, some participants with high titre responses appear to have lower trough concentrations and this trend is observed at week 12 and appears to hold for later weeks for some participants.

Observed donanemab serum trough concentrations versus treatment duration stratified by ADA titre cutoffs, for participants whose dose was escalated to 1400 mg every 4 weeks following 3 months of 700 mg titration are shown below. Higher ADA titre appeared after 16 weeks, and comparing different box plots for each week, it appears that higher titers were associated with reduction in observed trough serum concentrations.

Figure 22: Observed donanemab serum trough concentrations versus treatment duration for participants whose dose was escalated to 1400 mg every 4 weeks following 3 months of 700 mg titration in study AACI by titre categories.



Abbreviations: AACI = Study 15T-MC-AACI; conc = concentration; N = number of samples; TE ADA- = treatment-emergent antidrug antibody negative; Q4W = every 4 weeks.

In summary, PopPK modelling was conducted. Higher ADA titre appeared after 16 weeks, and comparing different box plots for each week, it appears that higher titers were associated with reduction in observed trough serum concentrations.

PopPK model

The selected base model had two compartments following IV infusion, with interparticipant variability on CL, as well as central and peripheral volumes of distribution. Clearance and distributional clearance were scaled allometrically by weight and central and peripheral volumes of distributions were also scaled allometrically with weight, using exponents of 0.8 for clearance terms and 1 for volume terms. The final model includes covariate effect of titre change over time on clearance.

Shrinkage on all parameters for the final model was estimated to be below 18%, except V1 where it was higher (37%). Although the shrinkage on V1 was high, it was deemed acceptable in the context of all other parameters meeting the criteria. Where titre value information was not available (37% of PK samples), the titre value was modelled using last observation carried forward method.

Between-participant variability on population V2 was high (94%), which may lead to higher variability and uncertainty around predicted trough concentrations (Ctrough,ss), reflecting the observed data.

A summary of post hoc parameter estimates by study has been provided. The parameter values are comparable between studies. This indicates that the study was not identified as a significant covariate.

Table 23: Pharmacokinetic and covariate parameters in population model.

Parameter	Base Model Population Mean (95% CI)[a]	Final Model Population Mean (95% CI)[a]
CL (L/h)[b]	0.0300 (0.0288, 0.0320)	0.0255 (0.0243, 0.0271)
V1 (L)[c]	3.40 (3.35, 3.44)	3.36 (3.31, 3.40)
V2 (L)[d]	4.48 (3.94, 5.25)	4.83 (4.26, 5.73)
Q (L/h)[e]	0.0196 (0.0166, 0.0247)	0.0200 (0.0163, 0.0248)
Covariate effects		
Covariate effect on CL[f]		
Effect of titer	NA	0.0487 (0.0436, 0.0552)
Between-participant variability CV% (95% CI)[a, g]		
CL	28.6% (26.6, 30.4)	24.9% (23.1, 26.8)
V1	18.7% (14.6, 23.1)	18.7% (14.7, 22.7)
V2	74.6% (67.2, 81.5)	93.9% (81.8, 109)
Residual unexplained variability		
Proportional (%)	46.9% (45.5, 48.2)	44.4% (43.3, 45.4)
Additive (ng/mL)	94.0 (79.4, 109)	91.5 (79.5, 106)

Abbreviations: CI = confidence interval; CL = clearance; CV = coefficient of variation; NA = not applicable; V1 = volume of distribution, central compartment; V2 = volume of distribution, peripheral compartment; Q = intercompartment clearance; WT = weight at baseline.

Note: numbers specified in the relationships below refer to the final model.

[a] 95% CI from bootstrap.

[b] $0.0255 * (WT/72)^{0.8}$.

[c] $3.36 * (WT/72)^{1.0}$.

[d] $4.83 * (WT/72)^{1.0}$.

[e] $0.0200 * (WT/72)^{0.8}$.

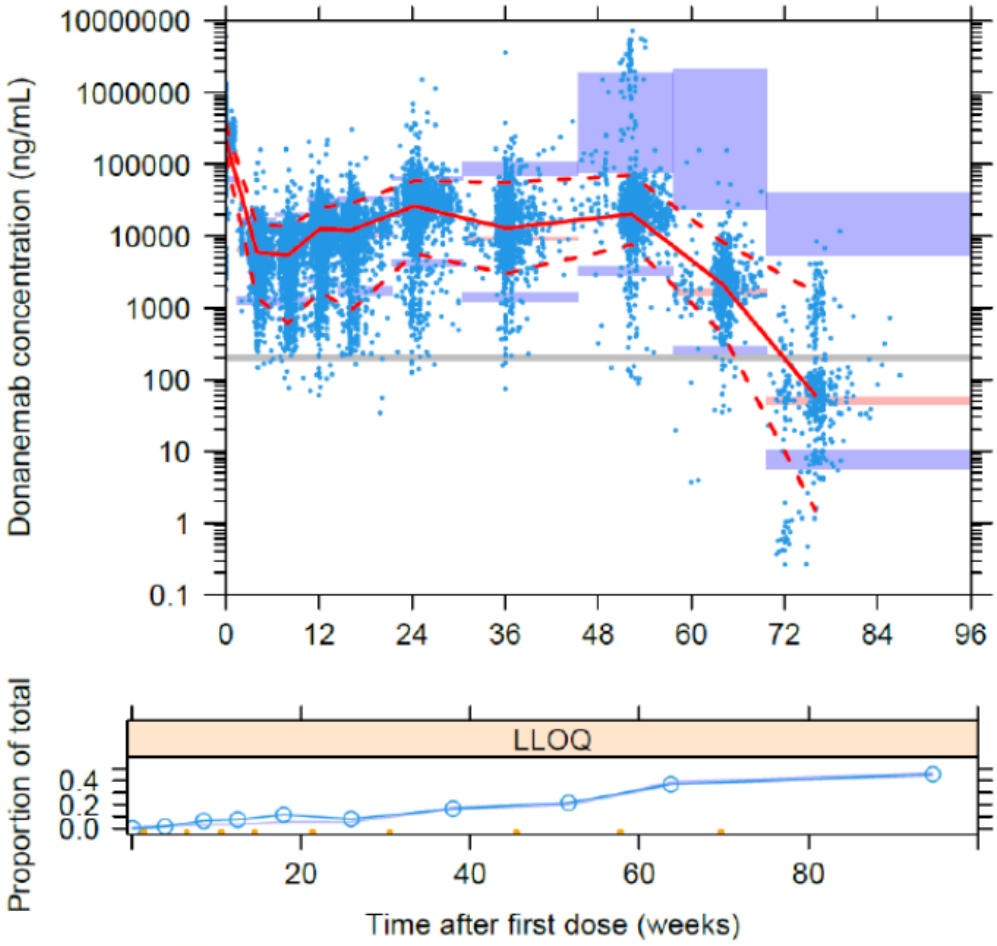
[f] $0.0255 * (WT/72)^{0.8} * (1 + ((0.0487 * \ln(titer(t)))$.

[g] Between-participant variability was calculated using the following equation for log-normal distributions of the random effects $\%CV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the parameter.

Eta shrinkage base model: CL = 12.4%, V1 = 38.2%, V2 = 21.8%.

Eta shrinkage final mode: CL = 15.1%, V1 = 36.7%, V2 = 17.9%.

Figure 23: Visual predictive check for donanemab final model.



Solid red line: median of observed concentrations; dashed red lines: 5th and 95th percentiles of observed concentrations; red shaded area: confidence interval (CI) for the median of simulated data; blue shaded areas: 95% CIs for the 5th and 95th percentiles of simulated data; blue full circles: individual observed concentration data. The gray horizontal line represents the lower limit of quantification (LLOQ) of 200 ng/mL. Bottom panel: the proportion of concentration data below the LLOQ vs time. The blue area represents the 95% CI of the proportion of simulated concentrations below the LLOQ, and yellow ticks are data binning. In the simulation, LLOQ data were modeled using the M3 method. Visual predictive check based on time from last administered dose could be found in Attachment 3.

It was noted that in the visual predictive check for donanemab final model there is a reduction in donanemab concentration between weeks 60 and 72, while dosing was continued up to week 72 This was justified as approximately 50% of participants were administered placebo after Week 52 due to meeting amyloid plaque clearance criteria per study protocol. Serum donanemab concentrations were collected from all participants, including those where donanemab dosing was stopped at Weeks 24 and 52. Serum donanemab observations including those participants who were switched to placebo in a blinded manned, declined, as anticipated, and contributed to reduced exposure from Weeks 52 to 76. This is supported by Figure 23 showing the observed serum donanemab concentration versus time.

Based on the non-compartmental PK analysis, the clearance in patients with AD was 0.0321 L/h while the clearance based on popPK was 0.0255 L/h. The difference in the clearance was justified as mean (CV%) donanemab clearance from non-compartment PK analyses of Phase 1 studies (AACD and AACC) following doses within the therapeutic range (10 mg/kg to 20

mg/kg) is reported at 0.0264 L/h (45, n = 7). This value is consistent with estimated mean CL of 0.0255 L/h from population PK analysis with a larger sample size (n = 2131).
Estimated mean donanemab serum CL of 0.0321 L/h was reported at lower, subtherapeutic donanemab doses of 1 mg/kg in Study AACC. In this Phase 1 study, after single-dose administration from 0.1 to 3 mg/kg, the mean terminal elimination half-life was approximately 4 days, with lower estimated CL. The results may not definitively indicate nonlinear PK at these subtherapeutic doses, as many samples at later time points from the lower dose groups were below the lower limit of quantitation, preventing an accurate estimate of terminal elimination half-life.

The PK of donanemab is dose and time linear at the therapeutic dose range of 10 to 20 mg/kg. No accumulation of donanemab in serum was observed with the 10-mg/kg Q4W dose, as shown by the accumulation ratio (observed to be approximately 1). There was limited accumulation with the donanemab 20-mg/kg Q4W dose, with a mean accumulation ratio of 1.26.

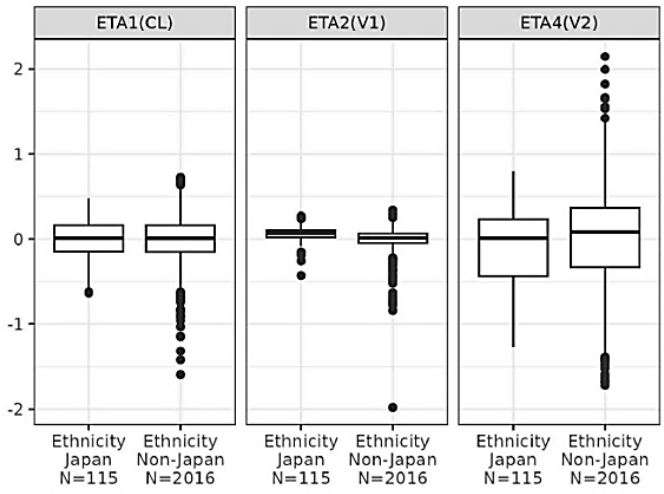
Special populations
It was stated that donanemab PK was not influenced by age (54 to 88 years at study entry), gender (55.0% female), race (89.9% white, 6.3% Asian, 2.9% black and 0.3% American Indian or Other), Cockcroft-Gault creatinine clearance (8.1 to 179.9 ml/min) or APOE ε4 carrier status (66.4% positive).

Detailed covariate evaluation using a stepwise covariate model resulted in these potential covariates not meeting the predefined forward/backward selection criteria.

Age, APOE ε4 genotype, gender and renal function did not explain the between-subject variability of serum clearance, central volume of distribution, and peripheral volume of distribution using the final popPK model. It can be concluded that they do not influence the exposure of donanemab.

In the popPK analysis, race and ethnicity were not identified as a significant covariate on any of the tested PK parameters. As an example, the following graph shows the lack of deviation in between-participant variability by Japanese and non-Japanese participant serum clearance, and central and peripheral volumes of distribution, which were similar between Japanese and non-Japanese participants.

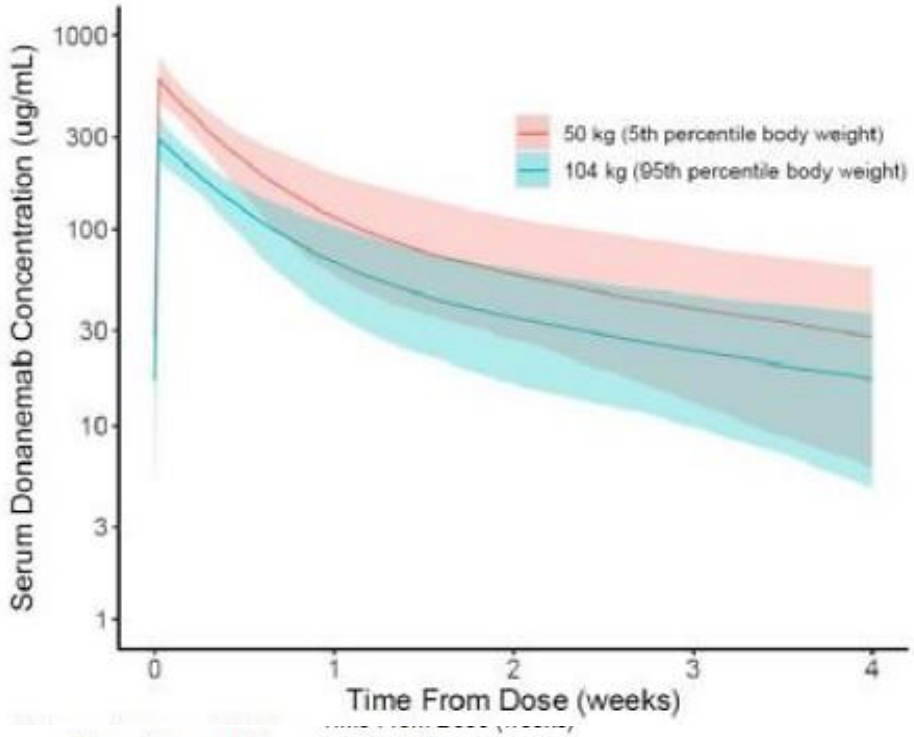
Figure 24: Analysis of ethnicity as a covariate.



Body weight was identified as a significant covariate on total body and distributional clearances, as well as central and peripheral volumes of distribution. Body weight increases clearance and volume of distribution following typical allometric relationships. Heavier patients are expected to have higher clearance and volume of distribution leading to lower overall exposure.

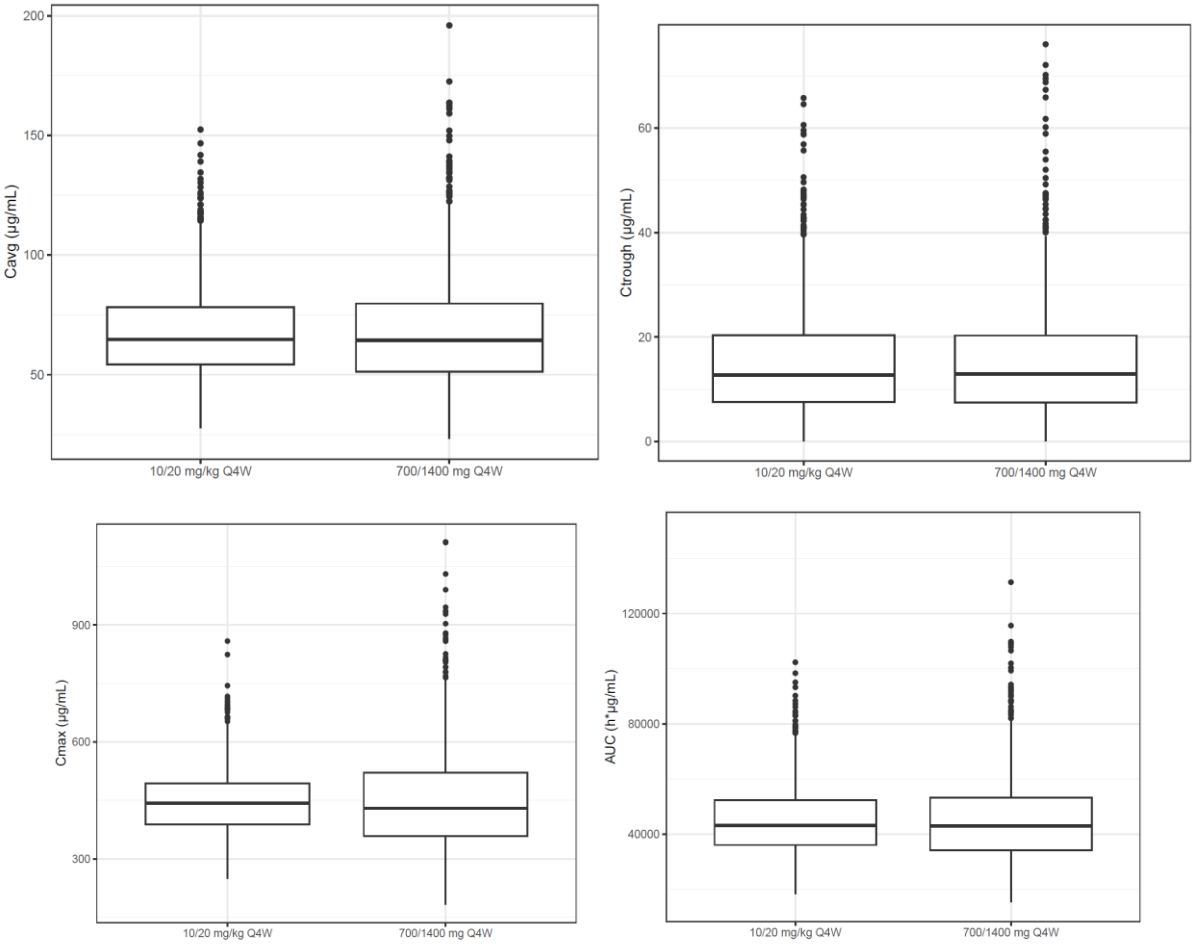
The clinical relevance of body weight on exposure is expected to be minimal. Changing from weigh based (in study AACD) to flat dosing (studies AACG, AACH and AACI) and shown through PK simulations, resulted in no meaningful changes in AUCτ,ss, Cmax,ss, Cav,ss or trough concentrations at steady state. These results shown that both approaches performed similarly, and flat dosing is recommended for donanemab.

Figure 25: Simulated relationship between serum donanemab concentration and body weight at steady state (1400 mg Q4W).



Abbreviation: Q4W = every 4 weeks.
Solid line represents median predicted concentration-time profile. Shaded regions represent 90% prediction intervals.

Figure 26: Body weight impact using simulations with final population PK model for maximum concentration (top left panel) trough concentration (top right panel), and exposure (AUC; bottom panel) at steady state.



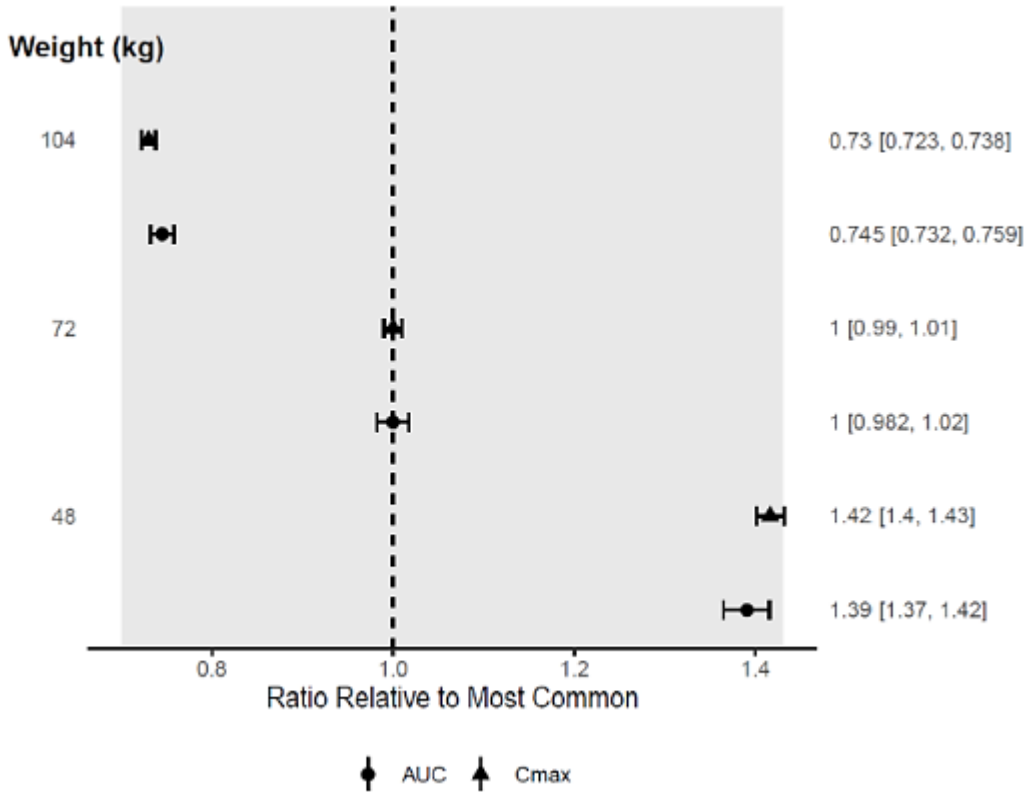
$C_{av,ss}$ = average drug concentration under steady state conditions during multiple dosing

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; C_{trough} = drug concentration before the next dose; PK = pharmacokinetics; Q4W = every 4 weeks.

Forest plots of the effect of body weight on donanemab exposure are shown on the following page.

Impact of body weight (5th and 95th percentiles) compared with reference participant (50th percentile body weight, low titre) shows that body weight was a significant covariate on exposure. The applicant stated that a 30% difference in exposure (shaded area) was used to indicate clinical relevance and that this evaluation shows that impact of body weight was not clinically significant.

Figure 27: Effect of body weight on donanemab AUC and C_{max} at steady state (700 mg IV every 4 weeks for 3 doses, followed by 1400 mg IV every 4 weeks).



Weight is a statistically significant covariate but was not found to be clinically significant. Based on the data provided, no significant changes in $AUC_{t,ss}$, Cmax,ss, $C_{av,ss}$ or C_{trough} were observed between weight-based and flat dosing.

Simulated relationship between serum donanemab concentration and body weight at steady state has been performed for subjects weighing 50 Kg and 104 Kg. The observed 5^{th} to 95^{th} percentile range of body weight distribution from a large sample size (n = 2131) was 48 kg to 104 kg. Reported simulations and conclusions were focused on this body weight range, representing of 90% of the study participants. Participants with very low body weight are anticipated to achieve serum average exposure ($C_{av,ss}$) above that associated with amyloid plaque reduction and attain higher than typical $C_{max,ss}$. Although $C_{max,ss}$ was not associated with any safety endpoints, $C_{av,ss}$ was identified as a significant covariate on ARIA-E baseline hazard. The estimated ARIA-E risk due to $C_{av,ss}$, following donanemab therapeutic dosing regimen, is much lower in comparison to other identified risk factors, specifically APOE ε4 homozygote genotype and number of baseline microhaemorrhages (3 or 4).

Very low weight participants with similar ADA titres to high weight participants may be expected to achieve higher than average $C_{av,ss}$. At the 95th percentile of $C_{av,ss}$, the risk is estimated to be very low at 1.06 compared with 1.00 for those with median $C_{av,ss}$. Even at the maximum $C_{av,ss}$ (233 μg/mL), the estimated ARIA-E risk of 1.2 is lower compared with estimated risk from other identified factors.

Donanemab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous immunoglobulin G. Thus, hepatic impairment is not expected to influence the clearance of donanemab.

PK studies are not required in participants with decreased renal function for large proteins that are not expected to undergo glomerular filtration. Donanemab is a monoclonal antibody with a molecular weight of 145 kDa and thus, renal impairment is not expected to influence the clearance of donanemab

Additionally, in population PK analysis of donanemab, hepatic or renal function (as categorical covariates), as well as hepatic (alkaline phosphatase, AST, ALT, bilirubin) or renal (CGCL, continuous) function parameters were not identified as significant covariates on the PK of donanemab. Post hoc estimated $C_{max,ss}$ and AUC_{ss} by hepatic and renal function category are shown in Table 24.

For donanemab (with between-patient exposure variability of approximately 30%), a clinically significant difference in exposure between these groups would be exposure differences of more than 40%. Therefore, the decrease of hepatic or renal function is not expected to have a clinically significant influence on the PK of donanemab.

Table 24: Post Hoc Estimated $C_{max,ss}$ and AUC_{ss} by Hepatic and Renal Function Category.

	N	**$C_{max,ss}$[a] (µg/mL)**	**AUC_{ss}[a] (µg·hr/mL)**
Hepatic function [b]			
Normal hepatic function	2026	428 (23)	85000 (32)
Mild hepatic impairment	95	417 (21)	84500 (30)
Moderate hepatic impairment	6	409 (18)	86600 (43)
Severe hepatic impairment	NA	NA	NA
Renal function [c]			
Normal renal function	347	354 (21)	67300 (31)
Mild renal impairment	1021	412 (19)	81700 (27)
Moderate renal impairment	741	490 (20)	99500 (29)
Severe renal impairment	18	479 (23)	103000 (25)
Severe renal impairment (CLcr <15 mL/min)	2	415 (NC)	83600 (NC)

Abbreviations: AST = aspartate aminotransferase; AUC = area under the concentration versus time curve; CLcr = calculated creatinine clearance; C_{max} = maximum observed drug concentration; CV% = percent coefficient of variation; N = number of patients in the analysis population; NA = not applicable; NC = not calculated; TBI = total bilirubin; ULN = upper limit of normal.

[a] Calculated as parameters during dosing interval at steady state using donanemab dosing regimen of 700 mg × 3 every 4 weeks, followed by 1400 mg every 4 weeks.

[b] As determined by the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG). Classified as normal (TBI ≤ULN and AST ≤ULN), mild impairment ([TBI ≤ULN and AST >ULN] or [TBI >(1.0-1.5) × ULN with any AST]), moderate impairment (TBI >[1.5-3] × ULN), or severe impairment (TBI >3 × ULN).

[c] Classified as normal (CLcr ≥90 mL/min), mild impairment (60 mL/min ≤ CLcr <90 mL/min), moderate impairment (30 mL/min ≤ CLcr <60 mL/min), and severe impairment (15 mL/min ≤ CLcr <30 mL/min).

Note: Geometric mean (CV%)

A statement is included in the product information to reflect that the effect of severe hepatic and renal impairment on the exposure of donanemab has not been studied.

Antidrug antibody titre

Donanemab clearance increased linearly with log(ADA titre). At the highest titre (1:5242880) observed, median clearance increased by a maximum of 39% compared to the median clearance at low titre group (<1:5129, titre of 1:5).

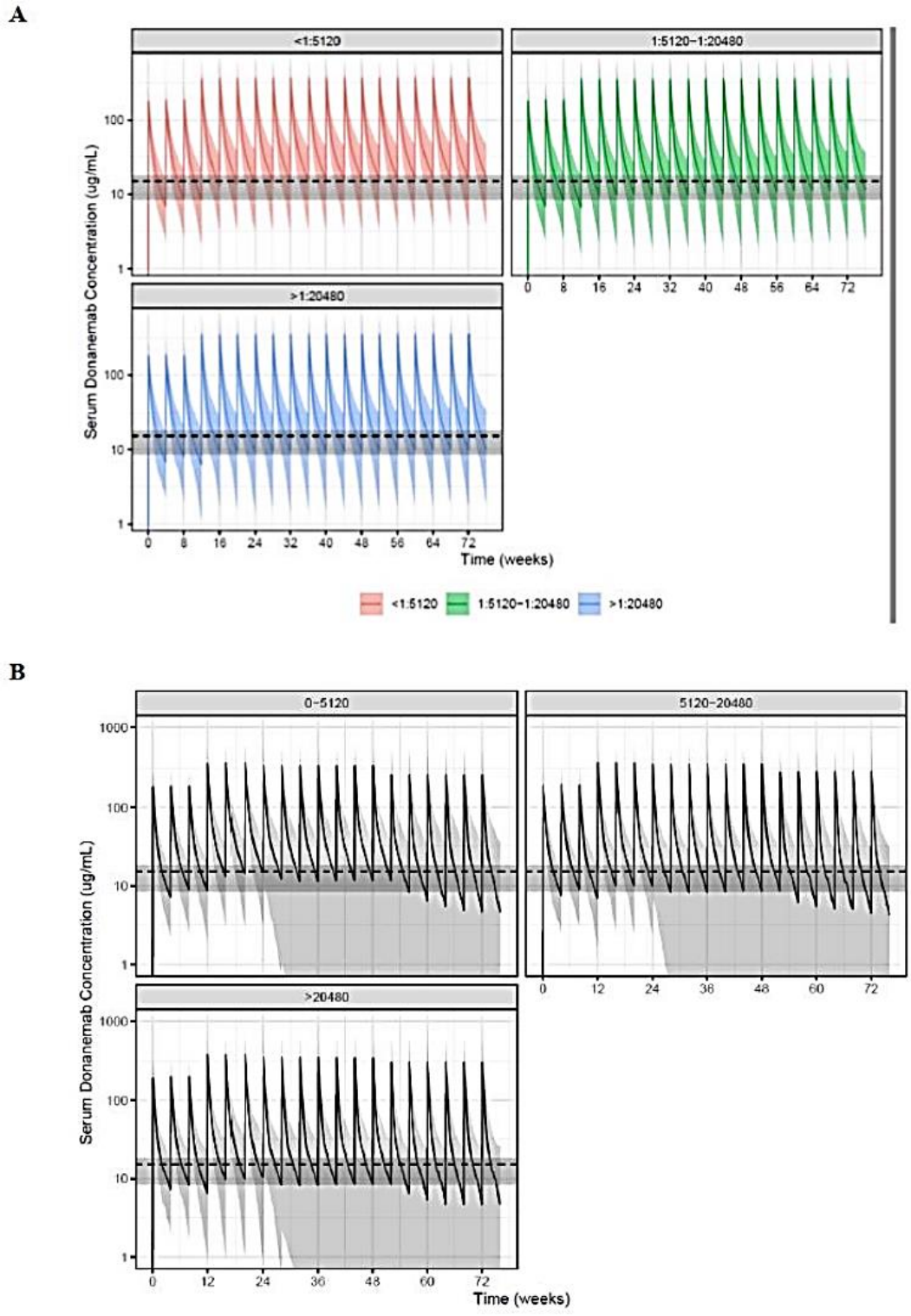
This increase in clearance with titre resulted in a 16% decrease in AUCτ,ss and a 31% decrease in drug concentration before the next dose (Ctrough,ss), comparing low (<1:5120) to high (>1:20480) titre group.

To assess the impact of titre on exposure, simulations were performed using the final population PK model using estimated between-participant variability and sampling from the observed distribution of titers. Two scenarios were simulated, in both sampling from observed distribution of titre varying over time and observed distribution of baseline body weight:

- One where participants followed donanemab dosing per protocols, with donanemab treatment cessation of participants who met the criteria for dose reduction to placebo, and
- Another, accounting for the worst-case scenario, where participants were assumed to stay on treatment to Week 76.

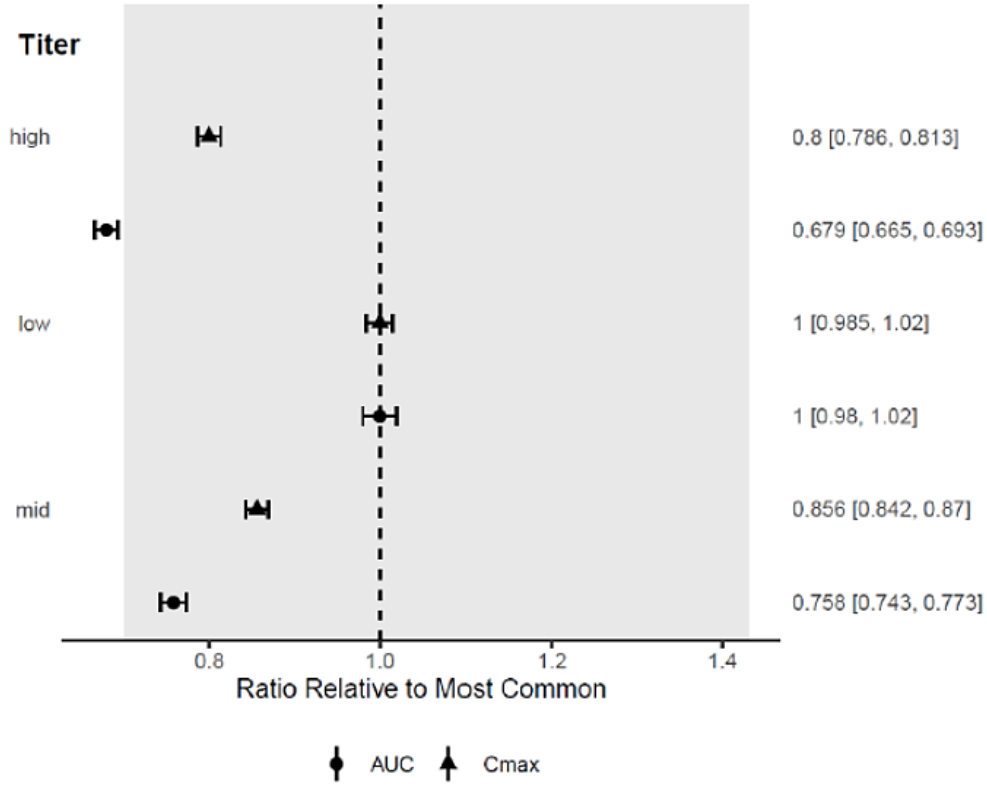
There was a significant overlap in concentrations across titers, even between extreme (1:20480) titre cutoff points. Most participants even under the worst-case scenario tended to maintain average concentrations above the threshold concentration associated with plaque reduction throughout the dosing interval. See Figure 28 on the following page.

Figure 28: Simulated donanemab concentration-time profiles according to the ADA titre categories. A: participants stay on treatment to Week 76 for representation purposes. B: participants followed donanemab dosing per protocols with donanemab dose cessation (and subsequent reduction in serum concentration) of treated participants who met the criteria for dose reduction to placebo, observed distributions of tier varying over time and baseline body weight.



Impact of ADA titre, which is a time-varying covariate on serum donanemab clearance, is shown compared with the reference participant at maximum titre effect (24 weeks)

Figure 29: Effect of covariates on donanemab AUC and Cmax at steady state on ADA titre (time-varying; maximum effect displayed) after titration (700 mg IV every 4 weeks for 3 doses, followed by 1400 mg IV every 4 weeks).



The percentage of participants across titers which maintained average concentrations above the threshold concentration associate for plaque reduction was provided. The vast majority (more than 90%) of participants maintained $C_{av,ss}$ above the threshold concentration (15.2 µg/mL) associated with plaque reduction.

IV.3 Pharmacodynamics

The following models were developed and analyses conducted to understand the pharmacodynamics of donanemab:

- Amyloid plaque model used to assess effects of donanemab in plaque reduction, time to plaque clearance, plaque re-accumulation and effect of APOE ε4 and ADA on plaque clearance
- P-tau217 and plasma GFAP models
- Exposure response relationships for efficacy, safety and immunogenicity
- Disease progression model used to explore exposure-response relationships for efficacy

Amyloid plaque model development

The target pharmacodynamic activity of donanemab is to reduce amyloid plaque. A total of 2023 participants from studies AACD, AACG, AACH and AACI combined were included in the analysis of amyloid plaque level.

An indirect response model was used to fit the amyloid plaque data (as measured using amyloid PET) over time in NONMEM 7.5.0 using the SAEM method. The model was parameterised in terms of degradation half-life of amyloid plaque, and individual patient baseline amyloid plaque level as an initial condition for response at time 0. For the final model development, a step wise forward-inclusion, backward-deletion process was used for covariate selection. Covariates tested on the half-life and baseline parameters included age, weight, ADA titre, TE ADA status, time from diagnosis, and baseline tau PET standardised uptake volume ratio (SUVR) as continuous relationships, and low/medium and high and APOE ε4 status as categorical relationships.

Following the completion of stepwise covariate modelling and additional covariate testing outside stepwise modelling, no statistically significant covariates were identified in the covariate analysis. The log (ADA titre) reduced serum donanemab concentration in a proportional and time-dependent manner, but no further influence of titre was found on amyloid plaque response. Bootstrap and VPCs supported the validity of the model.

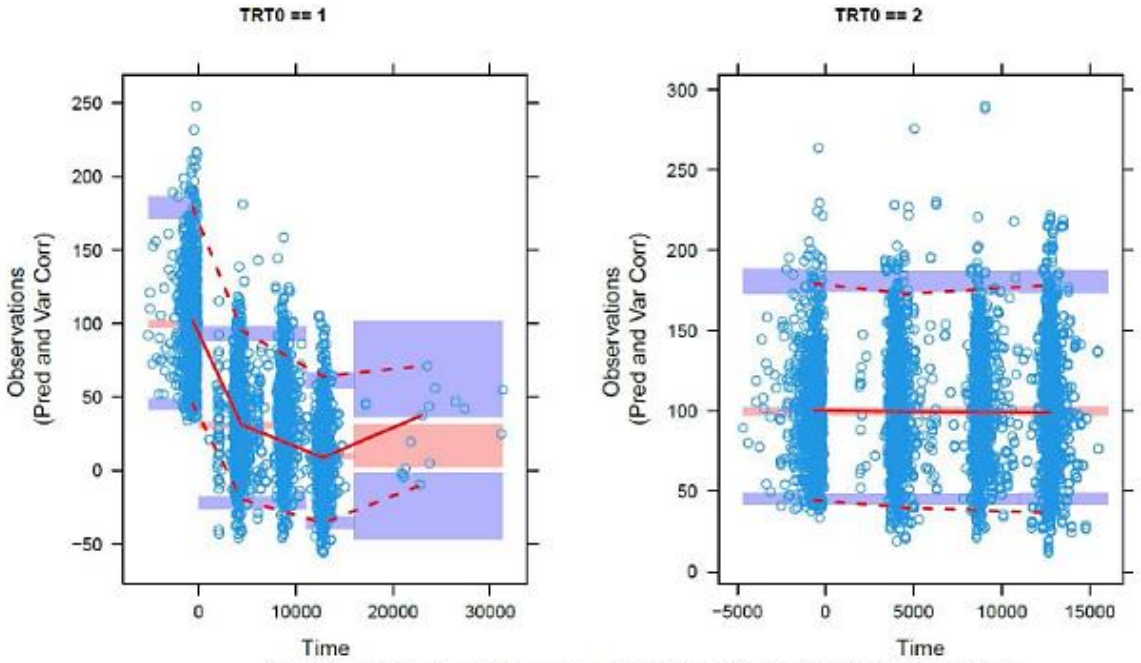
Table 25: Pharmacokinetic and covariate parameters in population amyloid plaque reduction model.

Parameter	Final Model (95% CI)[a]
Treatment effect	90.3 (45.0, 112)
Plaque removal half-life (hr)	151,000 (93,100; 184,000)
Baseline amyloid plaque (Centiloids)	101 (99.4, 103)
Baseline amyloid plaque box-cox transformation shape parameter	-0.576 (-0.737, -0.425)
Threshold concentration associated with treatment effect (µg/mL)	15.2 (8.54, 18.0)
Between-participant variability CV% (95% CI)	
Plaque removal half-life	74.6% (61.0, 83.4)
Baseline amyloid plaque	32.3% (30.7, 33.4)
Plaque scaler (SD in Centiloid)	23.0 (21.1, 26.2)
Residual unexplained variability	
Additive (Centiloid)	2.82 (2.33, 3.21)
Proportional (%)	13.8% (13.1, 14.4)

Abbreviations: CI = confidence interval; CV = coefficient of variation; SD = standard deviation.

[a] 95% CI from bootstrap.

Figure 30: Visual predictive check for amyloid plaque reduction final model.



Solid red line: median of observed concentrations; dashed red lines: 5th and 95th percentiles of observed concentrations; red shaded area: 95% confidence interval for the median of simulated data; blue shaded areas: 95% confidence intervals for the 5th and 95th percentiles of simulated data; blue full circles: individual observed amyloid plaque data. Data and predictions are stratified by placebo (right panel, TRT0 = 2) and donanemab treatment (left panel, TRT0 = 1). X-axis depicts hours and y-axis depicts Centiloids.

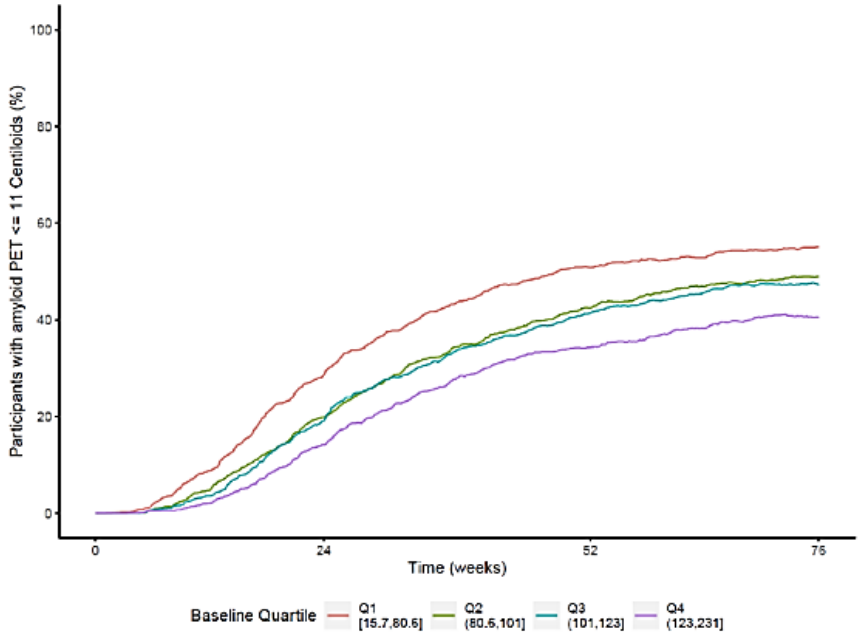
The model was used to examine effects of donanemab concentration on plaque reduction, effect of baseline amyloid on time to plaque clearance, effect of completing active treatment on plaque re-accumulation and effect of APOE ε4 and ADA on plaque clearance

It was determined that reduction of amyloid plaque was associated with maintaining a threshold of serum donanemab concentration above 15.2 mcg/ml (95% CI: 8.54, 18.0). In the covariate analysis no factor (including ADA status, titre or APOE ε4 carrier status) was found to have a significant impact.

The impact of baseline amyloid PET on time to achieve amyloid plaque levels below 11 Centiloids and amyloid plaque clearance (below 24.1 Centiloids) was investigated by simulating the change in amyloid load, given the dosing regimen and eligibility criteria for completing active treatment used in studies AACG, AACH and AACI.

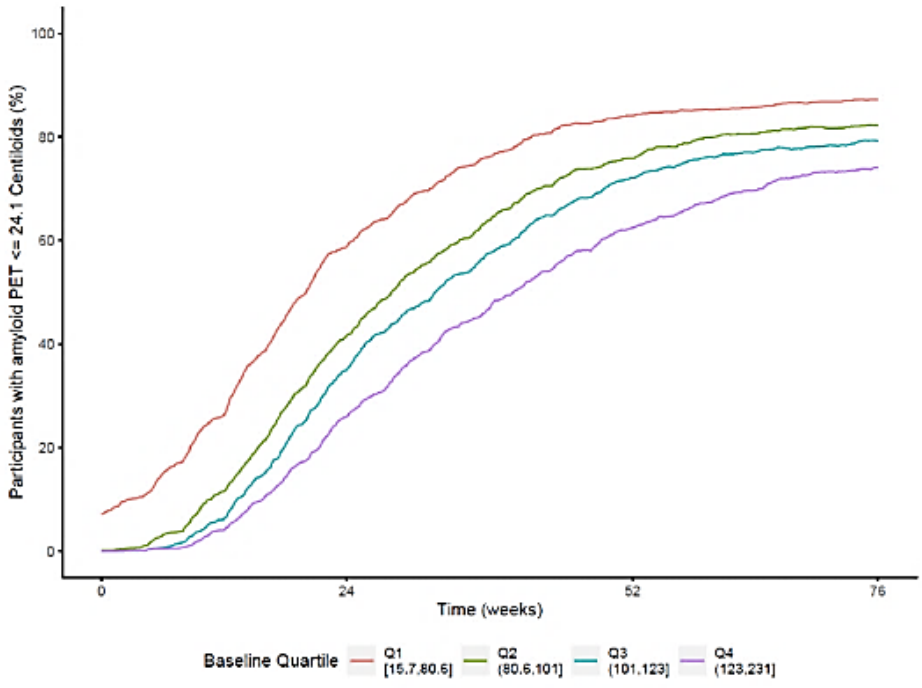
There is a separation between baseline quartiles, showing that time to achieve amyloid plaque levels below 11 Centiloids varied depending on the baseline value. Higher baseline values were associated with fewer participants achieving amyloid plaque levels below 11 Centiloids. Similar conclusions are made for plaque clearance (i.e., < 24.1 Centiloids).

Figure 31: Percentage of participants achieving amyloid plaque levels <11 Centiloids by duration on treatment and by quartiles of baselines amyloid PET assessed using treatment exposure-response model.



Abbreviations: NONMEM = nonlinear mixed-effects modeling; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetics; Q = quartiles.
Note: Patients were simulated to follow dosing treatment regimen, including the potential for down-titration based on Centiloids at Weeks 24 and 52, as described in the Methods section of the Population PK/PD report. Actual participants' titer time courses were sampled from the NONMEM dataset and last-observation-carried-forward applied to replicate the time-varying effect of titer on clearance in the PK model.

Figure 32: Percentage of participants achieving amyloid plaque clearance <24.1 Centiloids by duration on treatment and by quartiles of baseline amyloid PET assessed using treatment exposure-response model.



Effect of completing active treatment on plaque reaccumulation
The impact of completing active treatment on plaque reaccumulation and estimation of reaccumulation rate was investigated by simulation using treatment E-R model using previously established and published methods.

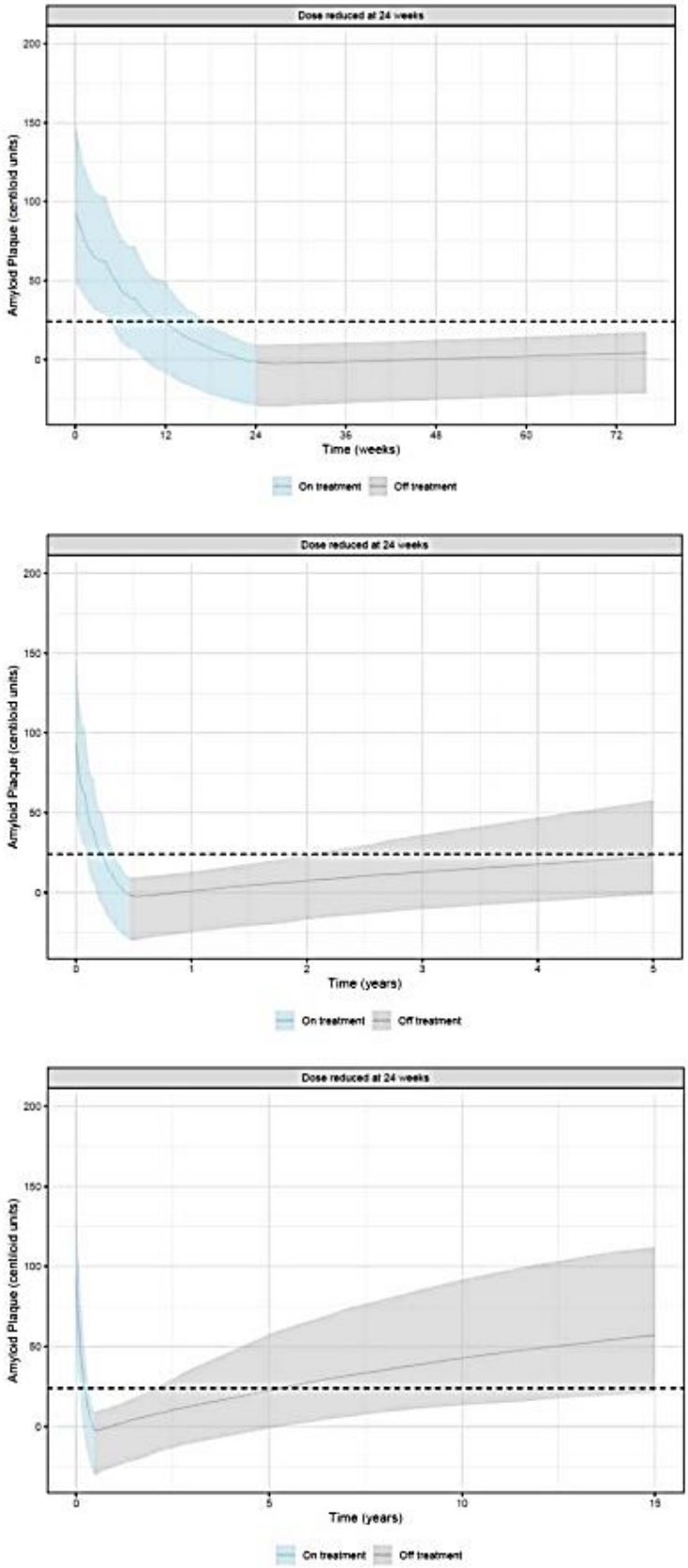
In the group of participants who achieved amyloid plaque levels below 11 Centiloids by 6 months (from studies AACG and AACI), completion of active donanemab treatment did not result in substantial increase in amyloid PET signal through to 1.5 years (end of studies) and further to approximately 3 years.

These groups of participants that provided the longest time-off treatment in the reported donanemab trials so far were assessed to estimate amyloid reaccumulation rate. With assuming a linear rate of increase over time beyond the observed period of 3 years, the same reaccumulation rate is applicable.

Based on study AACI, where approximately 80% of participants achieve amyloid plaque clearance (< 24.1 Centiloids) at 18 months, it is predicted to take 10 to15 years after last treatment for amyloid plaque levels to return to baseline, assuming linear increase over time. The amyloid reaccumulation rate is estimated at 2.90 (95% CI 2.16, 3.11) Centiloids per year.

This finding is supported by natural accumulation modelling studies showing approximately 3.3 Centiloids per year as the estimated rate of the natural amyloid accumulation model.

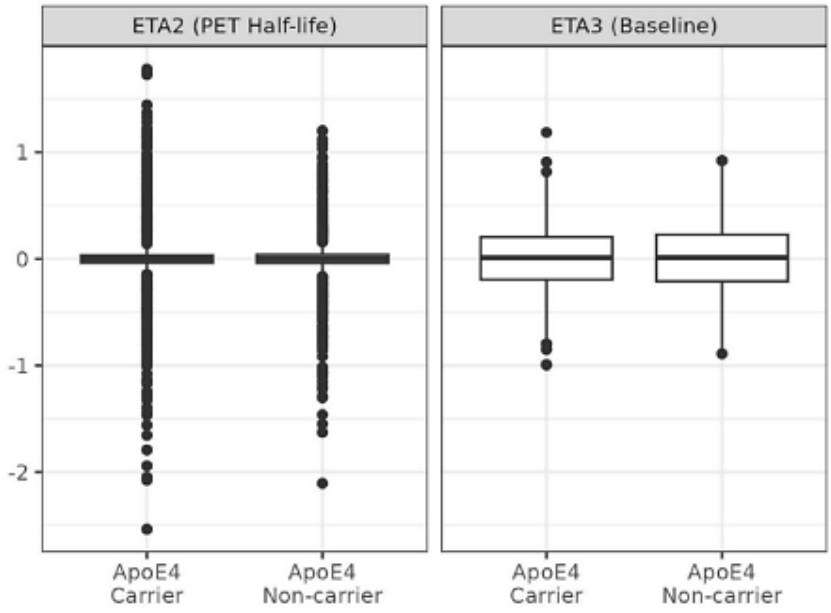
Figure 33: Amyloid plaque level over time using treatment exposure-response model, with between-participant variability included, stratified by those achieving less than 11 Centiloids at Week 24. Duration of 1.5 years (top panel) supported by data from Studies AACG and AACI, 5 years supported by data from Study AACH, Part C (middle panel) and extrapolated beyond the observed data range to 15 years (bottom panel).



Effect of APOE ε4 and ADA on plaque clearance

None of the investigated covariates, specifically age, weight, baseline tau, ADA titre, time from diagnosis, and APOE4 ε4 carrier status were identified as significant factors in the amyloid PET model. Individual predictions of amyloid PET baseline and overall effect were similar between APOE ε4 carriers and noncarrier. Lack of additional ADA titre effect may result from the appropriately selected dosing regimen, where even with faster donanemab clearance, most of the participants had serum concentration above the identified threshold concentration associate with amyloid plaque removal.

Figure 34: APOE ε4 carrier status did not explain/improve the between-participant variability (ETA2) of plaque estimated half-life (left panel) and baseline (right panel), using the final amyloid PET base model.



Abbreviations: Apoε4 = apolipoprotein subtype E allele 4; PET = positron emission tomography; participants with unknown carrier status (N=0.4) were grouped with carriers.
Lower and upper hinges correspond to 25th and 75th percentiles; The upper whisker extends from the hinge to the largest value no further than 1.5 × interquartile range.

Conclusions on the amyloid plaque model

The target PD activity of donanemab is to reduce amyloid plaque. An indirect response model was used to fit the amyloid plaque (as measured using amyloid PET) over time. No statistically significant covariates were identified. The log(ADA) titre reduced donanemab concentration in a proportional and time-dependent manner, but no further influence of titre was found on amyloid plaque response. Reduction of amyloid plaque was associated with maintaining a threshold of serum donanemab concentration above 15.2 mcg/ml. Higher baseline PET values were related with fewer participants achieving amyloid plaque levels below 11 Centiloids and plaque clearance <24.1 Centiloids). The amyloid reaccumulation is estimated at 2.90 Centiloids per year. ApoE ε4 and ADA were found not to affect plaque clearance.

P-tau217 model development and Plasma GFAP model development

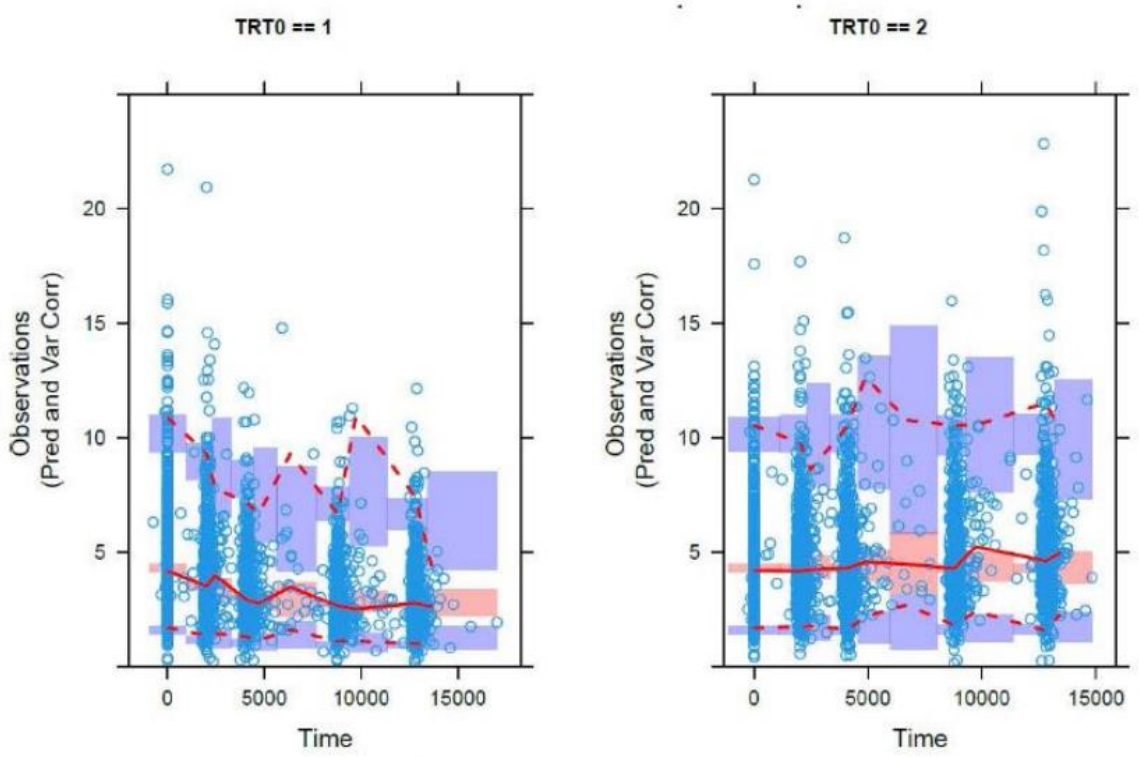
An indirect response model was used to fit the plasma tau phosphorylated at threonine 217 (P-tau217) data over time using the FOCEI method.

Individual post hoc participant parameters from the final PK and the amyloid plaque models were added to the P-tau217 dataset to obtain predicted drug concentrations and amyloid plaque levels for individual patients. The model was parametrised in terms of individual participant baseline P-tau217 concentration and estimated rate of P-tau217 formation.

A treatment-effect model driven by dosing information of donanemab was tested, with the effect of donanemab described as reducing the rate of P-tau217 formation. The impact of change in amyloid PET was evaluated as a predictor of P-tau217 reduction. Covariates were tested on the baseline P-tau217 concentration.

The covariates tested were age at entry, APOE ε4 carrier status, gender, race, weight at entry, presence of TE ADA, time since onset of symptoms of AD, time since diagnosis of AD and baseline tau PET SUVR.

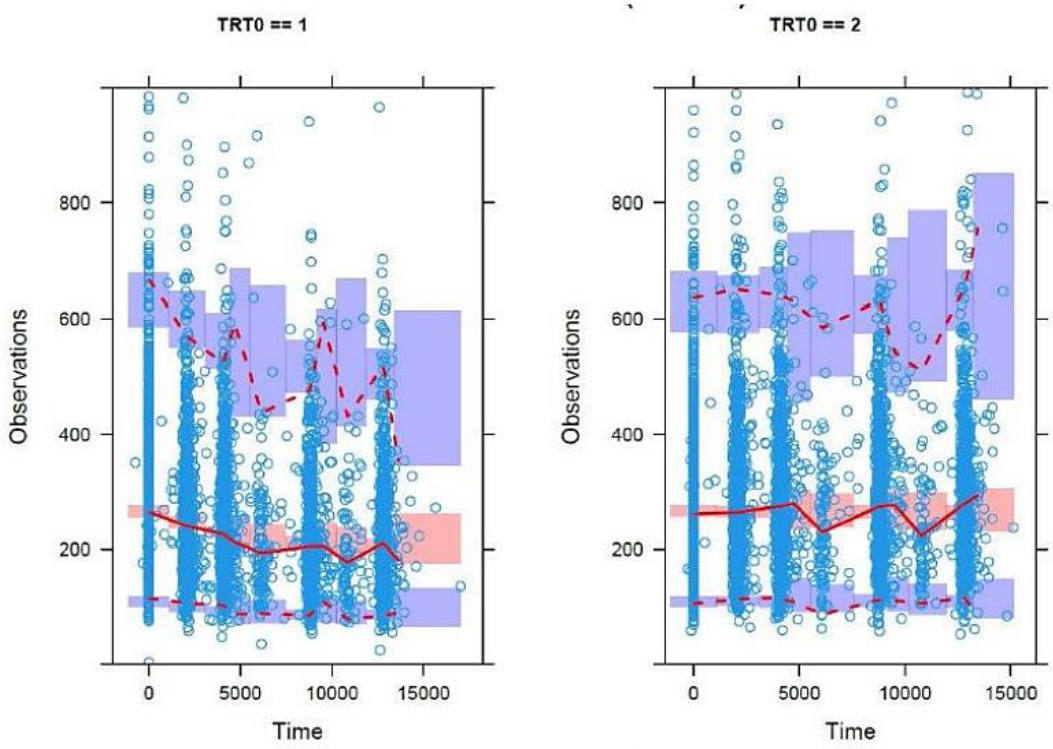
Figure 35: Visual predictive check of final P-tau217 model.



Abbreviation: P-tau217 = tau phosphorylated at threonine 217.
The points are the observed P-tau217 concentration in pg/mL plotted across time from first dose in hours. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles. TRT0==1 is donanemab treatment and TRT0==2 is placebo.

A basic indirect response model with placebo and on treatment data where donanemab treatment alter the production of glial fibrillary acidic protein (GFAP) was used to fit the GFAP data over time using the FOCEI method. A model where donanemab decreased amyloid load and reduced the rate of GFAP formation described the data well. Covariates were tested on the baseline GFAP concentration were age at entry, gender, weight at entry, eGFR, baseline MMSE, baseline tau PET SUVR and baseline P-tau217. No covariates were found to have a significant decrease in the variance of baseline GFAP concentration.

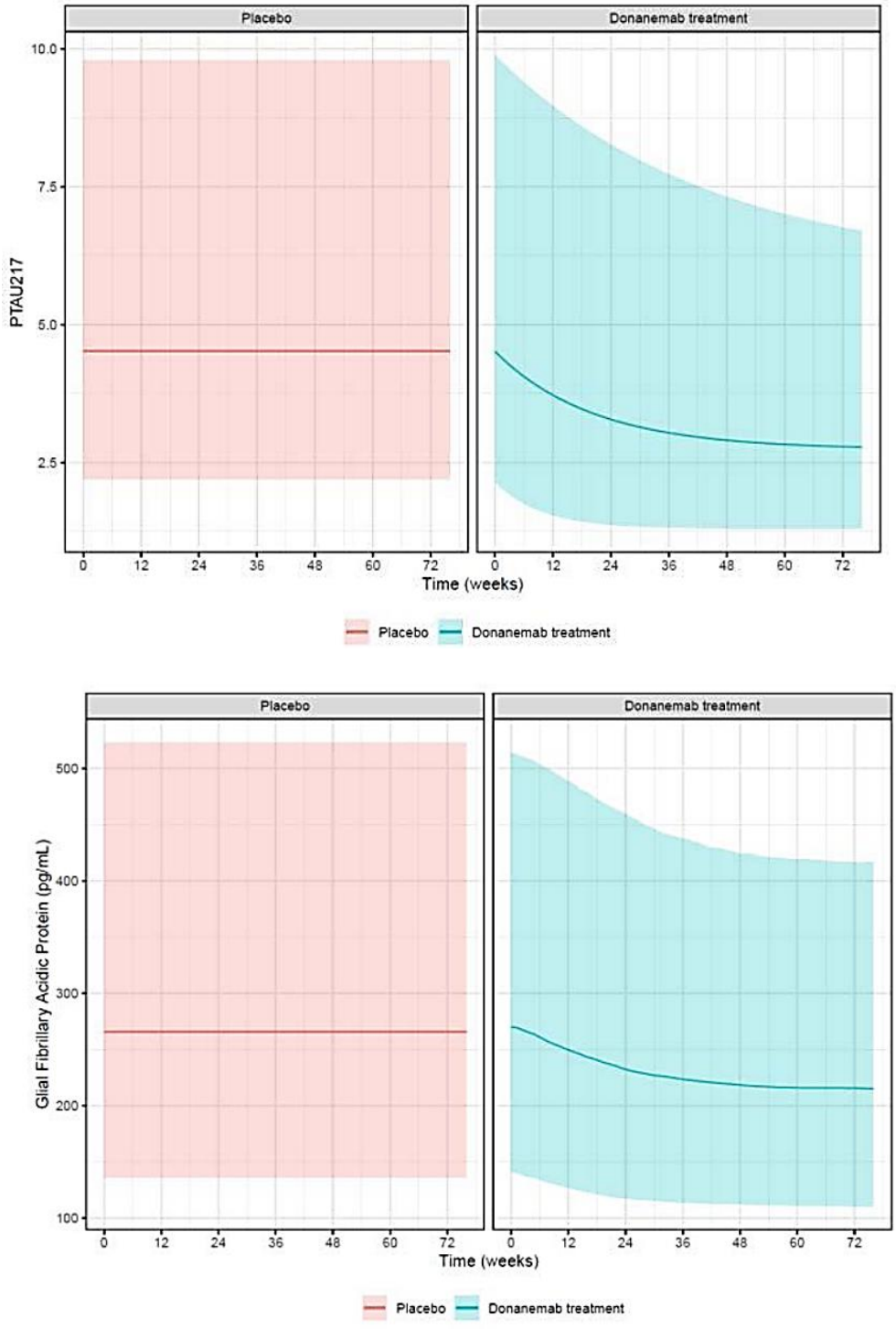
Figure 36: Visual predictive check of final plasma GFAP model.



Abbreviation: GFAP = glial fibrillary acidic protein.
The points are the observed plasma glial fibrillary acidic protein concentration in pg/mL plotted across time from the first dose in hours. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles. TRT0==1 is donanemab treatment and TRT0==2 is placebo.

These models were used in simulated analyses of plasma P-tau217 and GFA levels, as these biomarkers are elevated in participants with Alzheimer's disease. Donanemab treatment decreased the concentrations of both biomarkers, decreasing their rate of synthesis compared with placebo. Reduction in amyloid load (a relative change from baseline) was associated with decrease in the presumed rate of GFAP formation.

Figure 37: Simulation from final plasma P-tau 217 and GFAP models for placebo and with donanemab.



In these simulations, donanemab treatment decreased the concentrations of both biomarkers (P-tau217 and GFAP), decreasing their rate of synthesis compared with placebo.

Exposure-response relationships

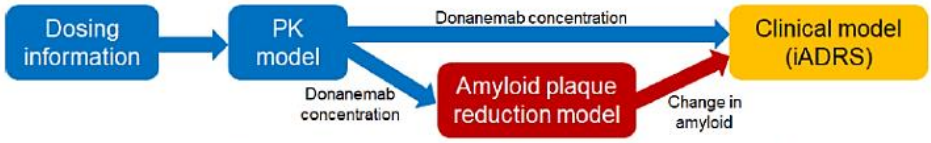
The popPK/PD analysis explored the relationship between donanemab treatment and one safety endpoint (ARIA-E) and two efficacy endpoints (iADRS and CDR-SB).

Exposure-response relationships for efficacy

The effect of donanemab on exposure was explored using a disease progression model. Separate models were developed for clinical dementia rating scale – sum of boxes (CDR-SB) and integrated Alzheimer's disease rating scale (iADRS).

Treatment effect models driven by dosing information of donanemab were tested as a predictor of disease progression. In addition, the impact of change in amyloid PET (absolute change from baseline or a relative change from baseline) was evaluated as a predictor of disease progression. Specifically, models where percent change from baseline in amyloid PET was a predictor of disease progression were assessed.

Figure 38: Schema for evaluation of models for iADRS and CDR-SB.

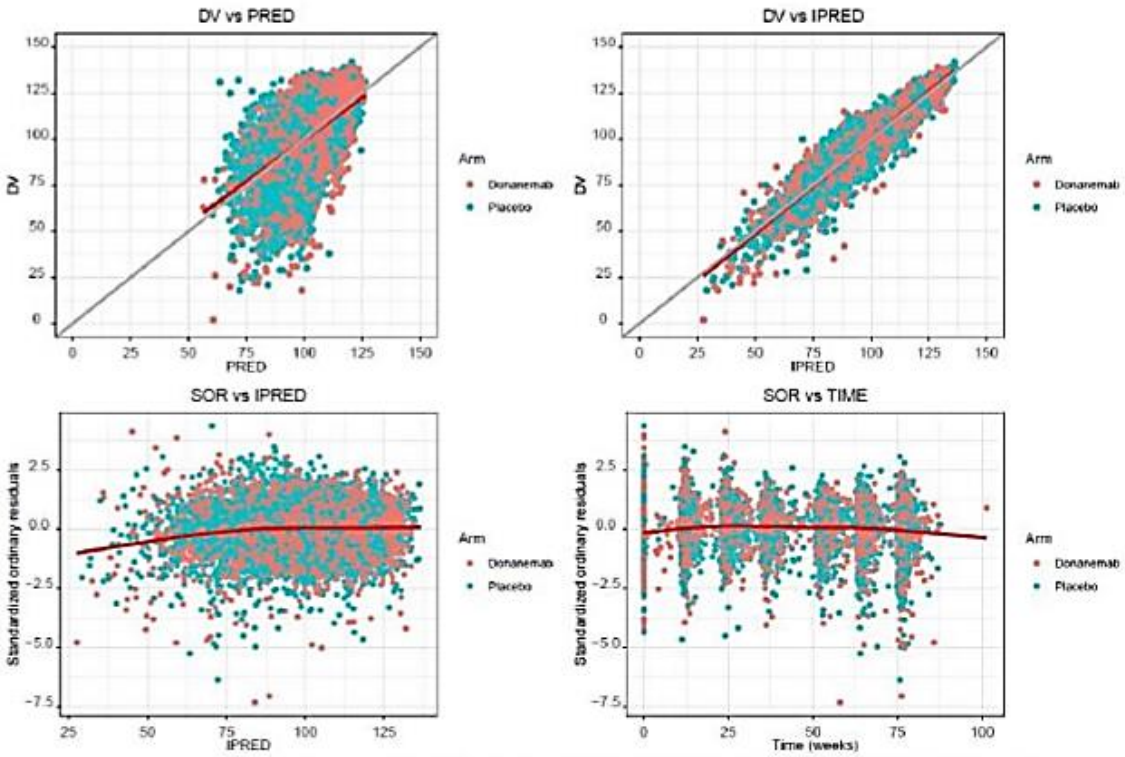


Abbreviations: CDR-SB = clinical dementia rating-sum of boxes; iADRS = integrated Alzheimer's disease rating scale; PK = pharmacokinetic.

Covariates were tested on various model parameters as shown below:

Model parameter	Covariates
Baseline estimate, Disease progression rate, and drug effect	APOE ε4 genotype, baseline tau PET SUVR, baseline amyloid PET, age of the study participant, time since onset of symptoms of AD, time since diagnosis of AD, baseline MMSE, TE ADA, ADA titer, sex, and body weight

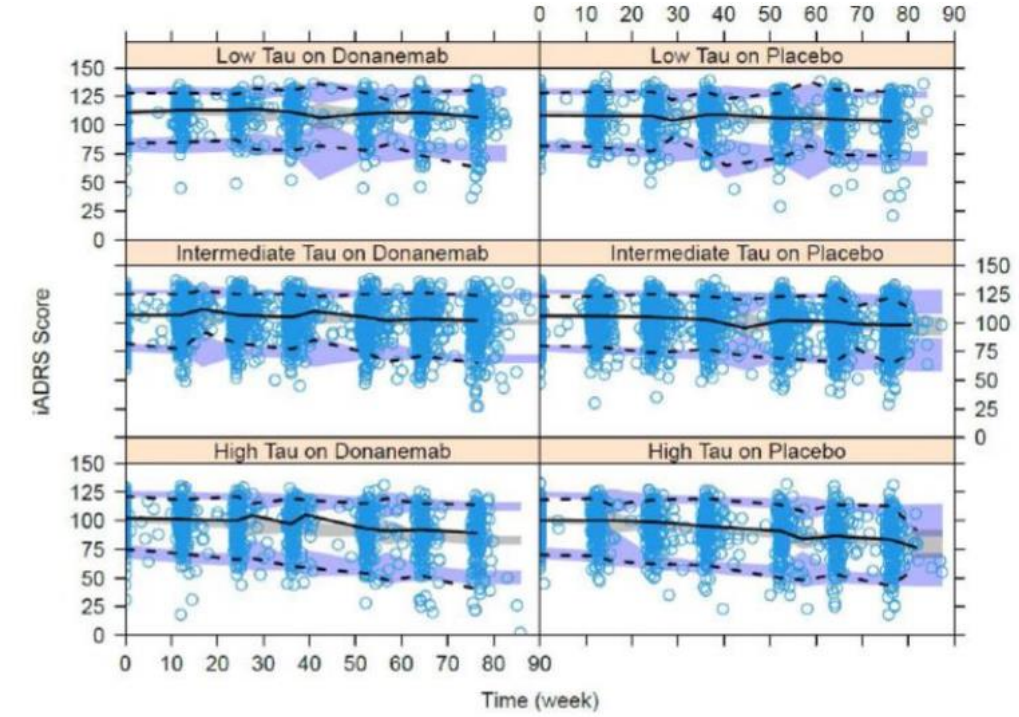
Figure 39: Goodness of fit for iADRS disease progression model.

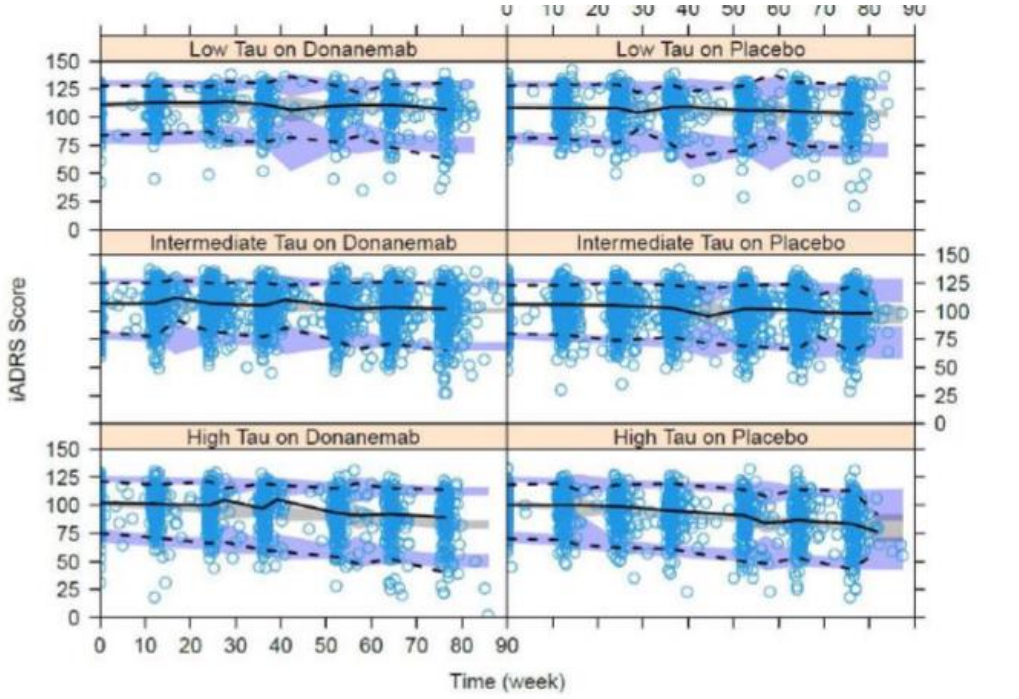


Abbreviations DV = dependent variable iADRS = integrated Alzheimer's disease rating scale; IPRED = individually predicted value; LOWESS = locally weighted scatterplot smoothing; PRED = population predicted values; SOR = standardised ordinary residuals.

LOWESS fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data are presented (black line) in addition to a line of identity (gray line on top panel).

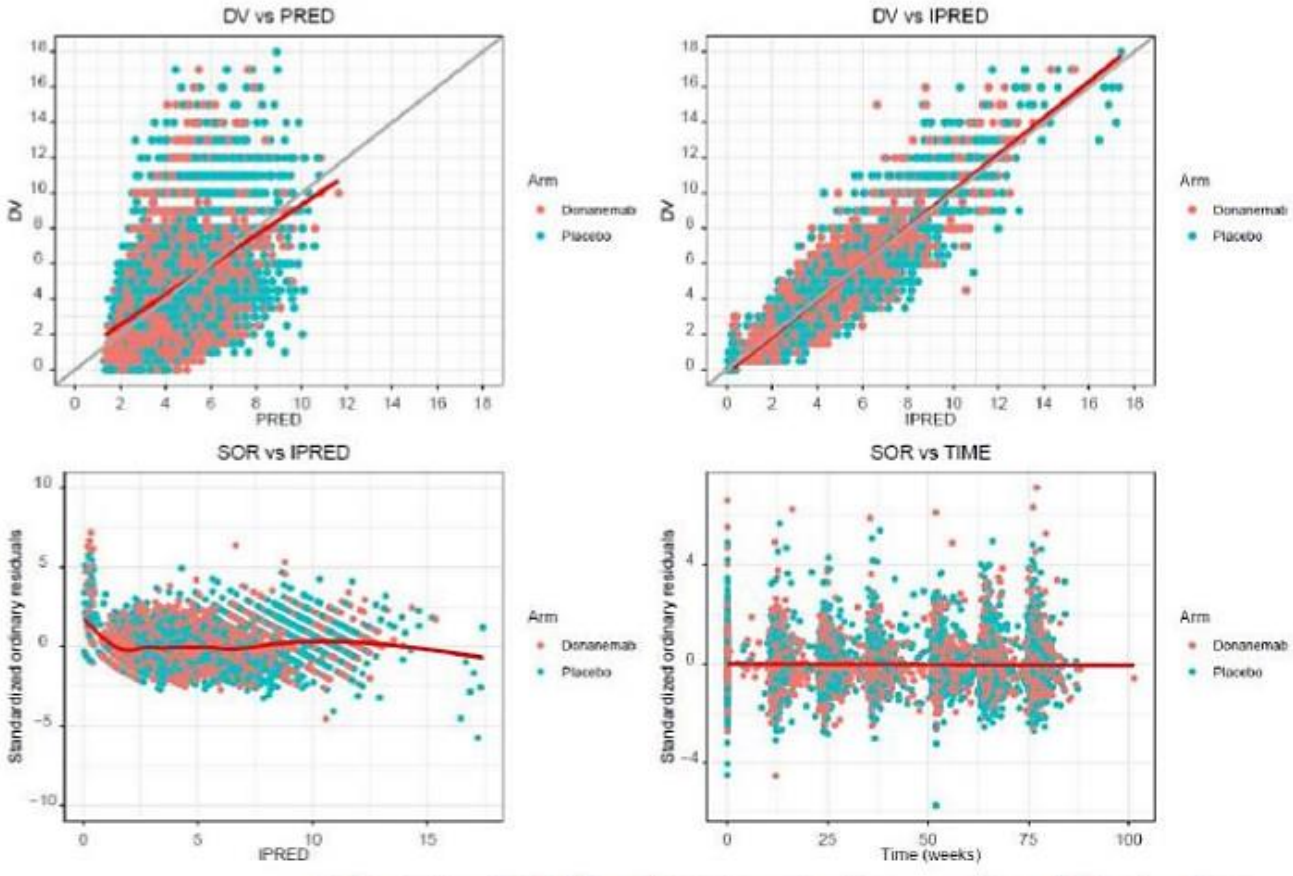
Figure 40: Visual predictive check of final iADRS disease progression model.





Abbreviations: AD = Alzheimer's disease; iADRS = integrated Alzheimer's disease rating scale; SUVR = standardized uptake value ratio.
Very Low Tau: <1.10 SUVR
Intermediate label = low/medium Tau: SUVR <1.10, with a topographic deposition pattern consistent with advanced AD (AD++), or ≤1.10 SUVR ≤1.46, with a topographic deposition pattern consistent with moderate AD (AD+).
High Tau: SUVR >1.46, with a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++).
The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.

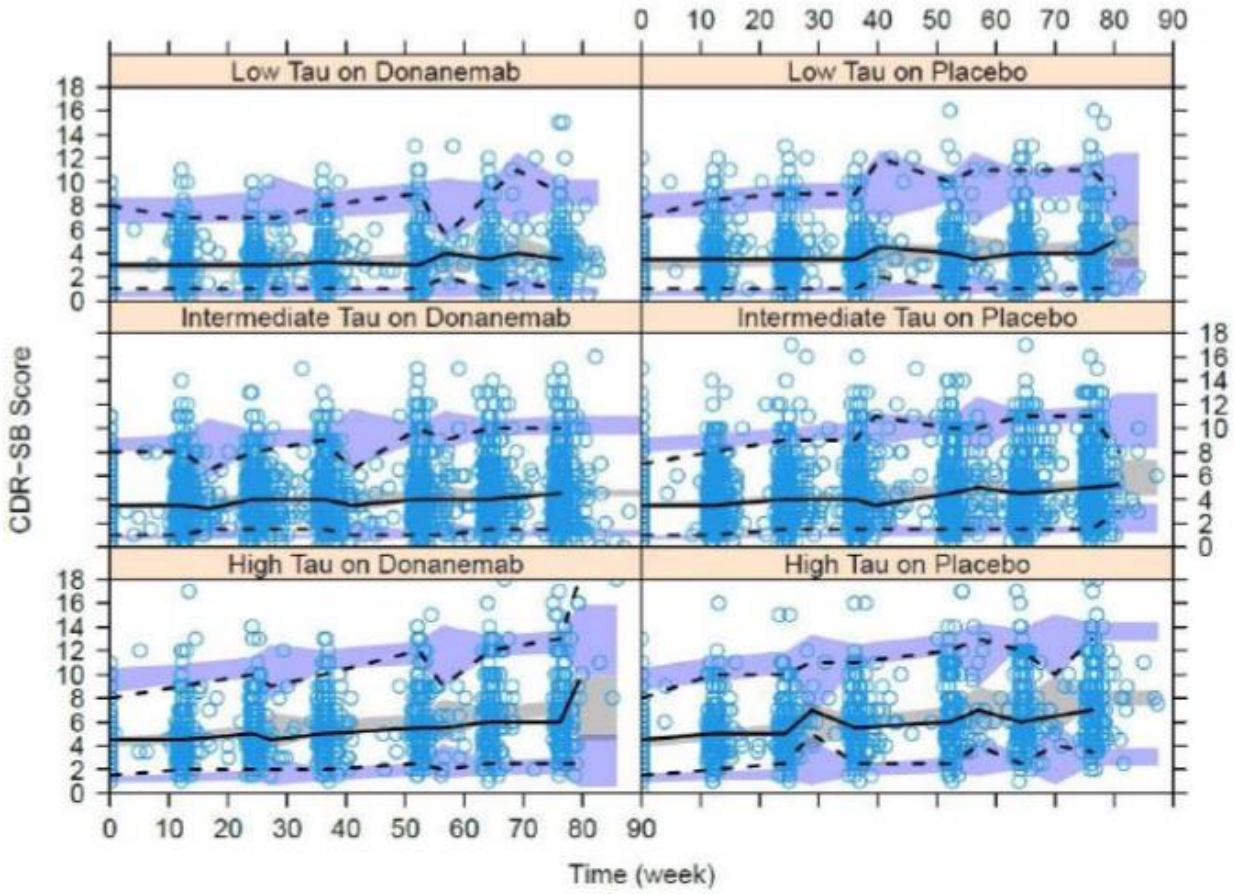
Figure 41: Goodness of fit for CDR-SB disease progression model.



Abbreviations: CDR-SB = clinical dementia rating-sum of boxes; DV = dependent variable; IPRED = individually predicted value; LOWESS = locally weighted scatterplot smoothing; PRED = population predicted values; SOR = standardized ordinary residuals.

LOWESS fit, a smoothed value given by a weighted linear least-squares regression over the span of observations, for data are presented (black line) in addition to a line of identity (gray line on top panel). Four participants with inconsistent observations were removed from these plots. For completeness, their observations are included in appendix plots.

Figure 42: Visual predictive check of final CDR-SB disease progression model.



Abbreviations: AD = Alzheimer's disease; CDR-SB = clinical dementia rating-sum of boxes; SUVR = standardized uptake value ratio.
Very Low Tau: <1.10 SUVR
Intermediate = low/medium Tau: SUVR <1.10, with a topographic deposition pattern consistent with advanced AD (AD++), or ≤1.10 SUVR ≤1.46, with a topographic deposition pattern consistent with moderate AD (AD+).
High Tau: SUVR >1.46, with a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++).
The points are the observed data. The lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas are the model-predicted 95% confidence interval of the corresponding percentiles.

Model applications

In the donanemab disease progression model exploring the impact of donanemab on clinical efficacy, there was a clear treatment effect of donanemab on clinical efficacy. Disease progression rate estimated using exposure-amyloid plaque-scores model on iADRS was reduced by 33.2% (p<0.001), while progression as measured by CDR-SB was reduced by 36.3% (p<001) in the low/medium tau population. In the combined population, disease progression rate on iADRS score was reduced by 29.3% (p<0.001). Treatment effects favouring donanemab were observed in all baseline tau participants though greater efficacy was observed in participants with low to medium tau, suggesting that treating patients earlier provides more benefit.

Simulations with the disease progression model were conducted to determine impact of baseline disease state (mild, MCI), tau population (combined and low/medium), and donanemab treatment cessation once amyloid plaque has been removed.

The simulations indicate the following:

- Significant treatment difference compared with placebo were observed in low/medium tau and in combined populations.
- The model-estimated treatment effect differed by baseline disease state
- The disease progression model demonstrated that donanemab slowed disease progression compared with placebo in
    - Combined population for participant with MCI and mild dementia using CDR-SB and iADRS scales
    - Low/medium tau population for MCI and mild participants on both CDR-SB and iADRS scales

Figure 43: Model predicted overall impact and of disease state (baseline MMSE) on disease progression on CDR-SB (top panel) and iADRS (bottom panel) sales in the combined population, for participants with MCI and participants with mild dementia due to AD.

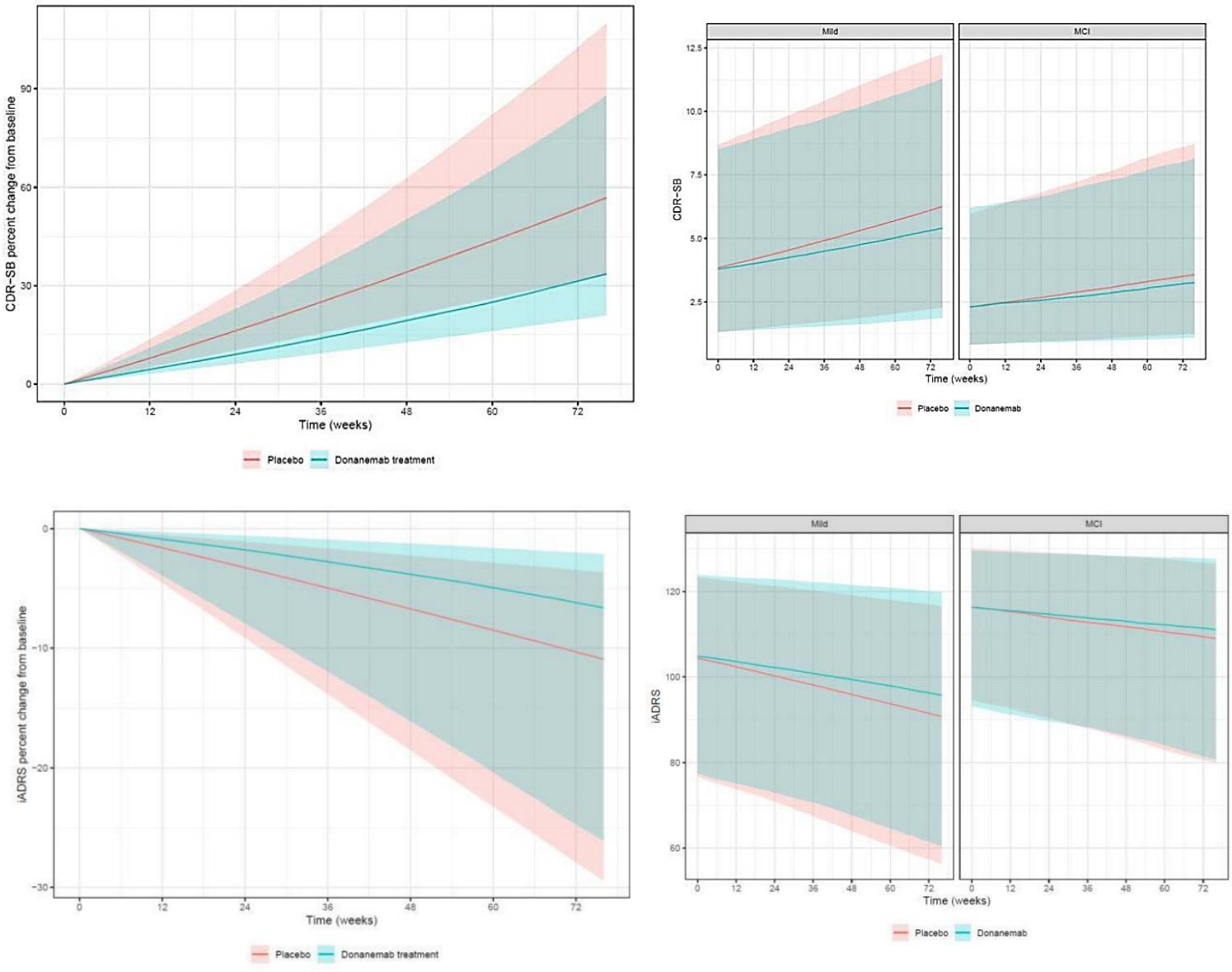
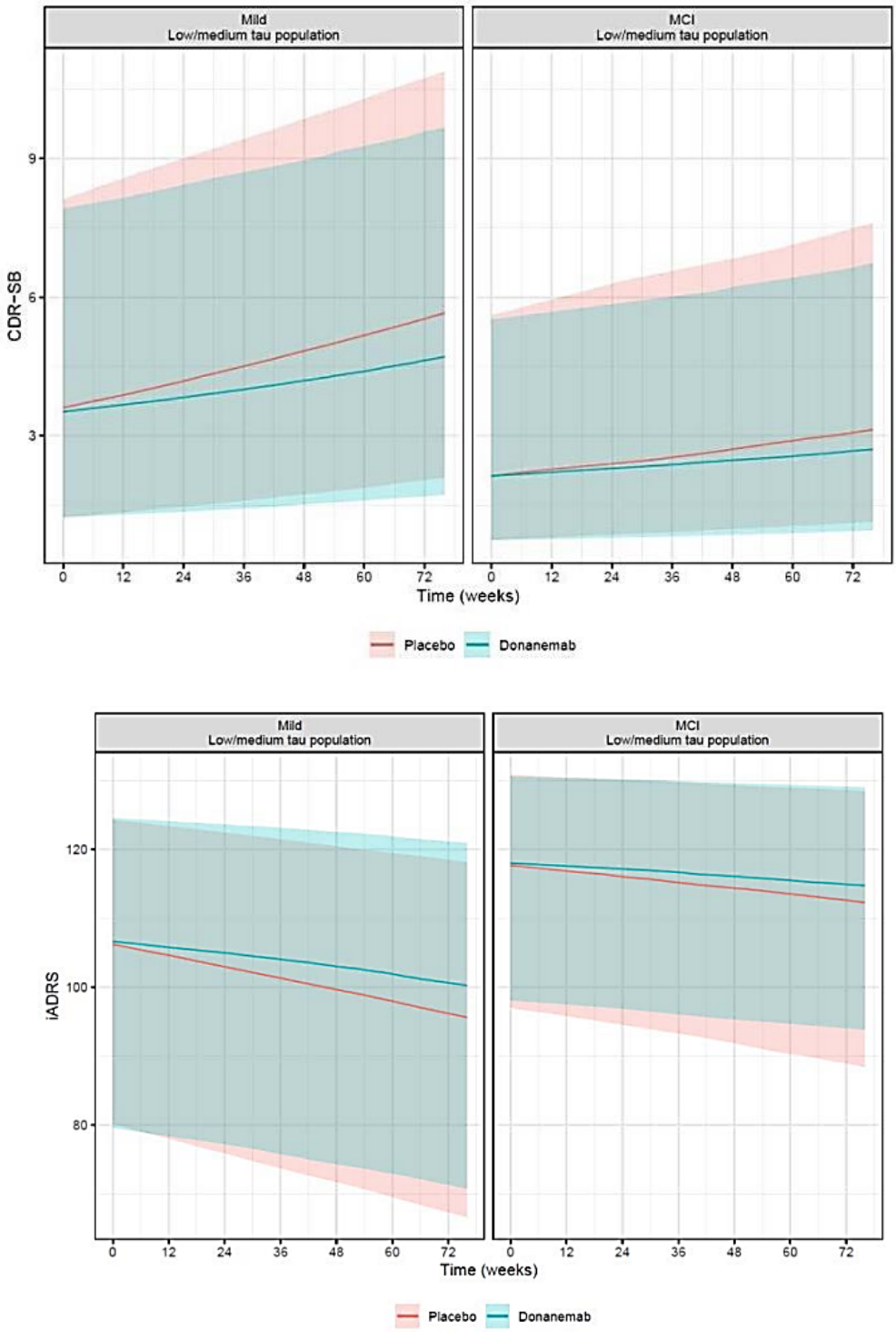
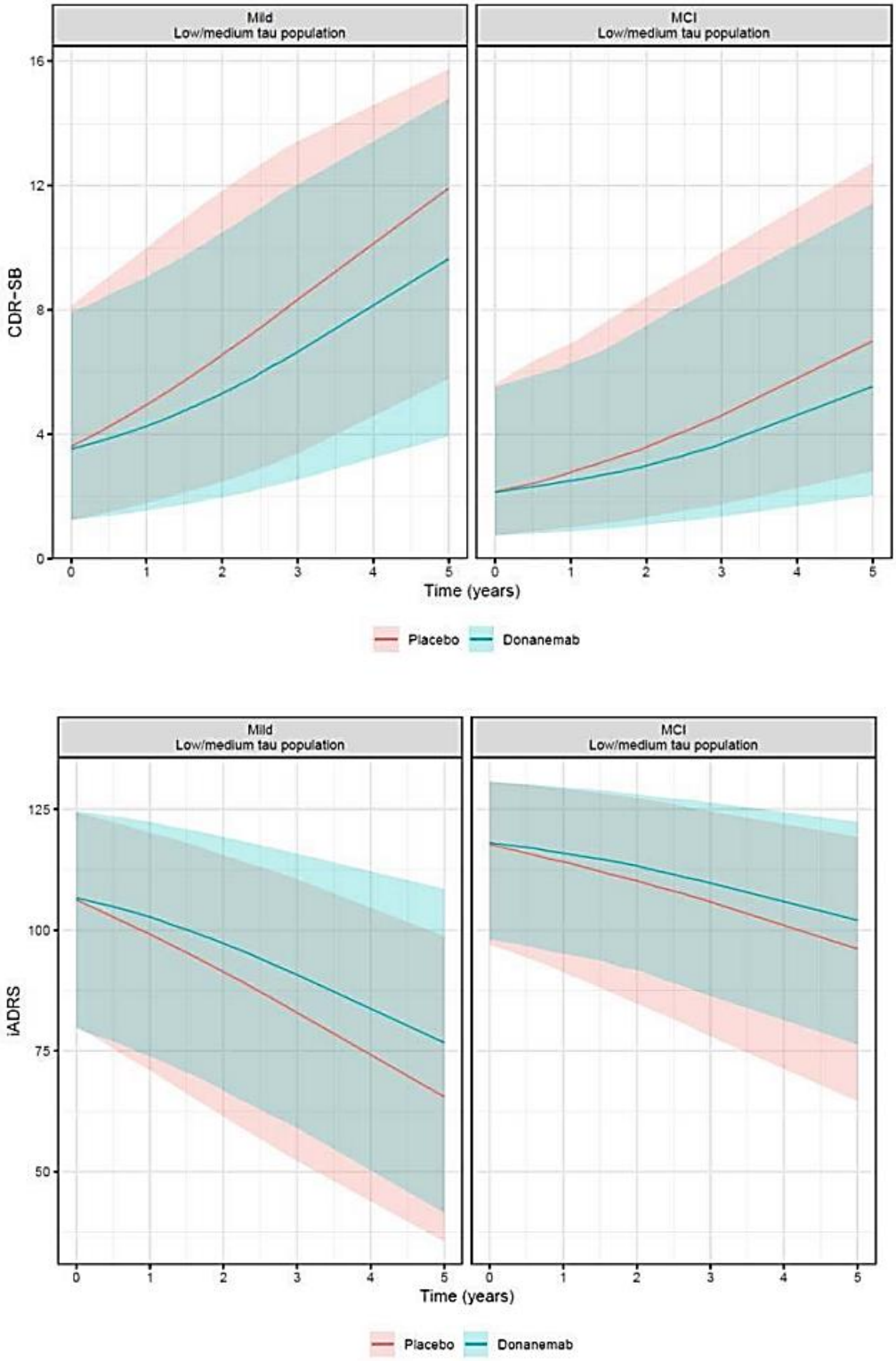


Figure 44: Model-predicted impact of disease state (baseline MMSE) on disease progression on CDR-SB (top panel) and iADRS (bottom panel) scales in the low/medium tau populations for participants with MCID and participants with mild dementia due to AD over the duration of Study AACI (Week 76).



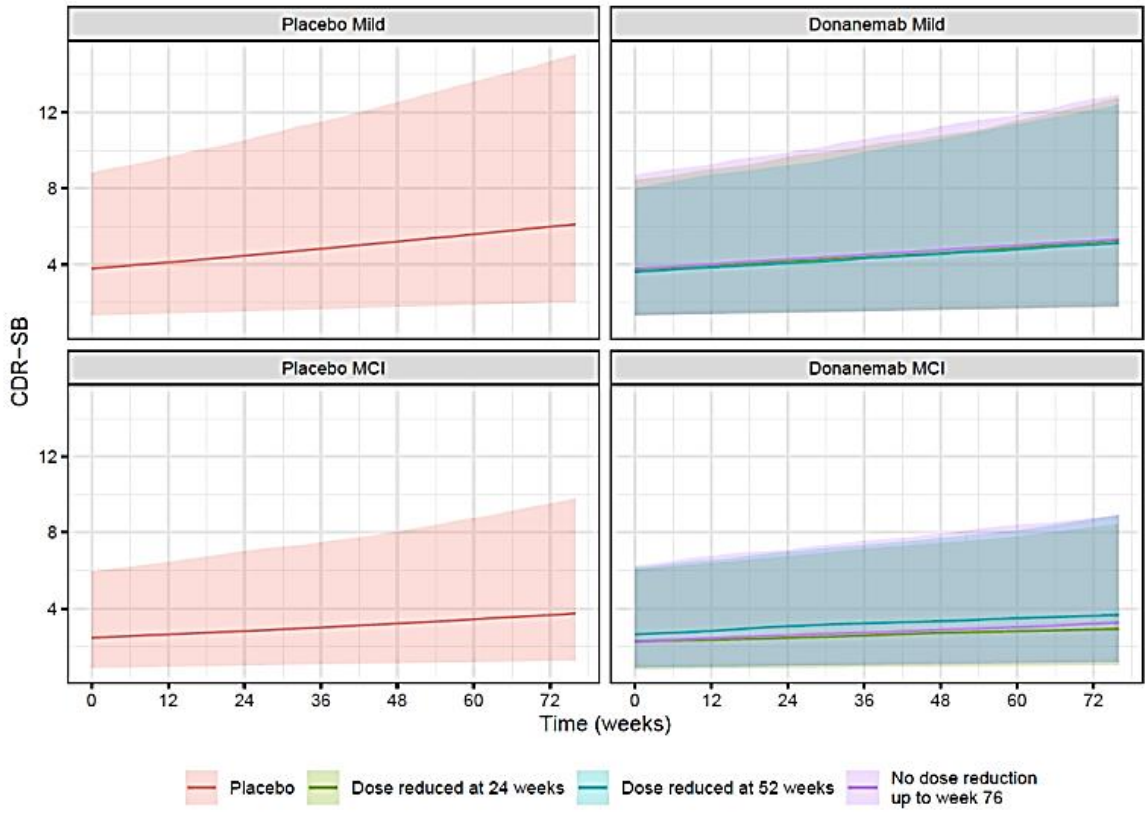
To further evaluate donanemab effect on disease slowing over time, simulations were conducted using the disease progression model, extending beyond the duration of study AACI (for up to 5 years) by assuming time linearity for disease rate. The simulations demonstrate that disease slowing, relative to placebo, increases over time.

Figure 45: Model predicted impact of disease state (baseline MMSE) on disease progression on CDR-SB scales for the low/medium tau population for participants with MCI and mild dementia due to AD on CDR-SB (top) and iADRS (bottom) scales.



Simulation results suggest that once amyloid is cleared, there is little impact of completing active treatment on clinical efficacy.

Figure 46: Model-predicted impact of duration of treatment on disease progression using exposure-amyloid plaque CDR-SB model in the combined population using CDR-SB scale.



Treatment effects favouring donanemab were observed in all baseline tau participant groups, though greater efficacy was observed in participants with low-medium tau suggesting that treating patients earlier provides more benefit. Simulations with the disease progression model, assuming linear disease progression rate, suggest that disease slowing increases over time compared to placebo.

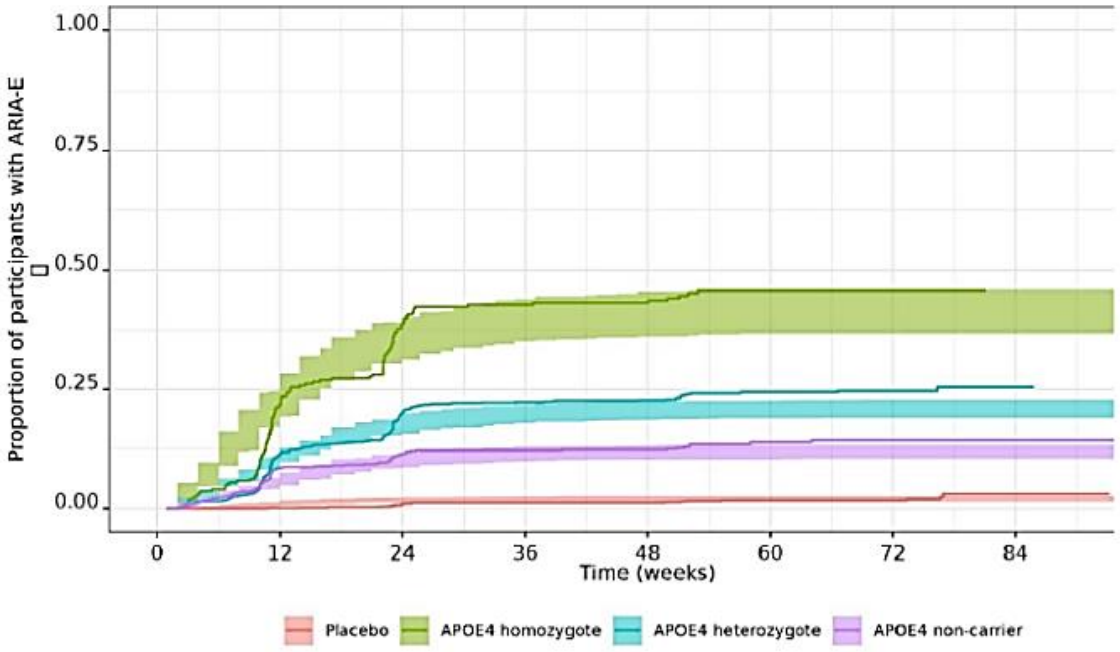
Exposure-response relationship for safety

A total of 2874 participants were included in the analysis of the time-to-first amyloid-related imaging abnormalities-oedema/effusions (ARIA-E) event.

For safety measurement ARIA-E (based on MRI or treatment-emergent adverse event cluster), there was a clear donanemab treatment effect. ARIA E hazard (that is instantaneous risk) is driven by the baseline hazard, donanemab treatment, APOE ε4 genotype, average concentration at steady state, number of baseline microhaemorrhages, and time components.

ARIA-E baseline hazard differed by APOE ε4 genotype, and by Week 24 it was 1.8 times higher in heterozygotes APOE ε4 as compared with noncarriers, 3.9 times higher in homozygotes APOE ε4 as compared with noncarriers, and 2.1 times higher in homozygotes APOE ε4 compared to heterozygotes APOE ε4.

Figure 47: Visual predictive check of final time-to-first ARIA-E event model.



Abbreviations: APOE4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusions.
Note: The solid lines are the Kaplan-Meier plot of the observed data, and the shaded areas are the 95% confidence intervals for the simulated data.

The number of baselines microhaemorrhages was identified as a significant covariate on baseline hazard. The baseline hazard for ARIA-E increased with the increase in number of microhaemorrhages. Donanemab average serum concentration at steady state (Cavg,ss) was identified as a significant covariate on baseline hazard. Participants with higher Cavg,ss have an increased risk of ARIA-E compared to those with median Cavg,ss. The baseline hazard for ARIA-E was 1.2 times higher in participants with the highest observed Cavg,ss (233 mcg/ml; 0.05% of the PK evaluable population) compared with those with median Cavg,ss (52.1 mcg/ml; 50% of the PK evaluable population).

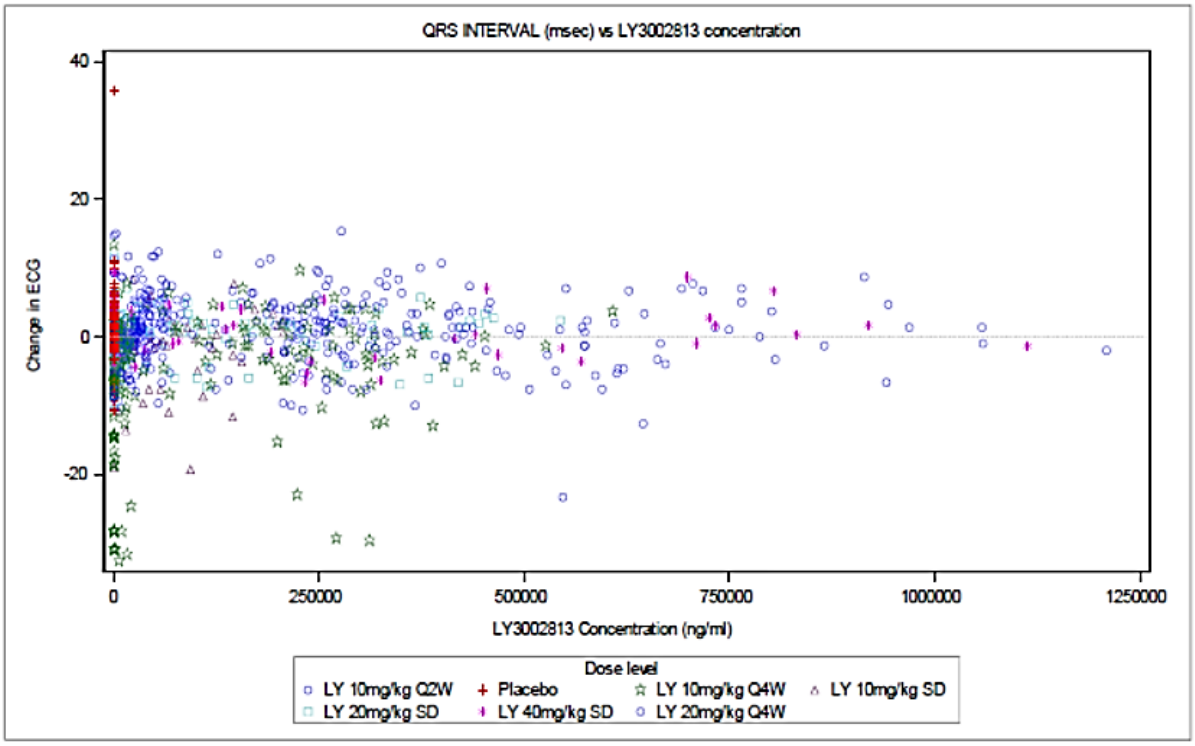
Although immunogenicity had an impact on PK, there was no significant impact of immunogenicity on risk of ARIA-E based on parametric time-to-first event analyses.

Amyloid-related imaging abnormalities (ARIA) E hazard is driven by the baseline hazard, donanemab treatment, APOE ε4 genotype, average concentration at steady state, number of baselines microhaemorrhages, and time components. For more information, please see the clinical safety section of this Public Assessment Report.

Exposure-response relationships with electrocardiogram parameters

<u>QRS duration</u>
The exposure-response analysis showed that there was no significant effect of donanemab concentration on the QRS duration across the observed exposure range in study AACD.

Figure 48: QRS duration versus donanemab concentration – Study AACD.

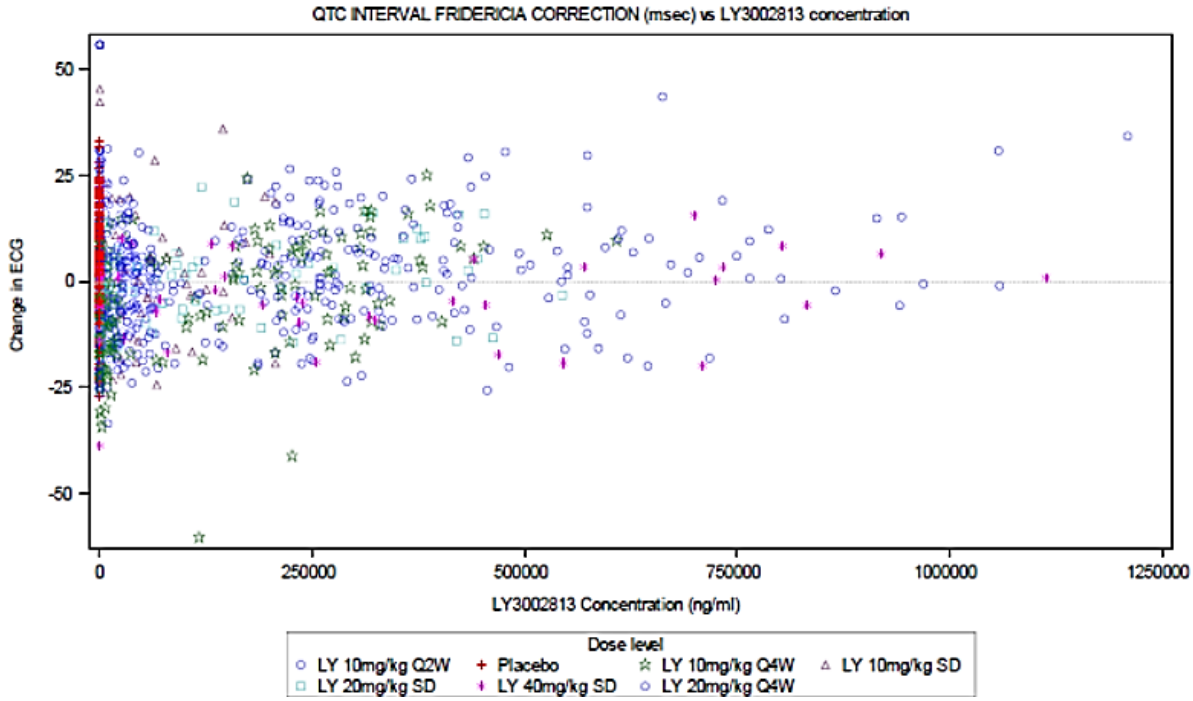


Abbreviations: BQL = below the limit of quantification; ECG = electrocardiogram; LY = donanemab; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = single dose.
Baseline is defined as Day 1, Infusion.
PK data imputation:
The concentration is set to 0 at all time points in placebo. The concentration is set to (in donanemab data with concentration <BQL 200 ng/mL.
The concentration is set to 0 in donanemab data with unavailable PK data that is predose.
The concentration is treated as missing in donanemab data with unavailable PK data that is postdose.

QTcF interval

There was no significant association between donanemab concentration and QTcF interval change from baseline across the observed exposure range in study AACD. For study AACG, based upon a predicted steady state Cmax of 454 mcg/ml (at a dose of 1400 mg Q4W), the predicted mean change in QTcF is expected to be –0.961 ms (90% CI: -2.01, 0.09). The result is consistent with QTcF across donanemab clinical studies AACD, AACG, and AACI-PC, where no significant QTcF prolongation was observed. These analyses indicate that donanemab has low risk for QTc prolongation.

Figure 49: QTcF interval versus donanemab concentration – Study AACD.



Abbreviations: BQL = below the limit of quantification; ECG = electrocardiogram; LY = donanemab; PK = pharmacokinetic; QTcF = corrected QT interval - Fridericia formula; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = single dose.
Baseline is defined as Day 1, Infusion.
PK data imputation:
The concentration is set to 0 at all time points in placebo. The concentration is set to 0 in donanemab data with concentration <BQL 200 ng/mL.
The concentration is set to 0 in donanemab data with unavailable PK data that is predose.
The concentration is treated as missing in donanemab data with unavailable PK data that is postdose.

Immunogenicity

Immunogenicity results presented are from the integrated analysis set comprising the placebo-controlled periods of studies AACG and AACI. Results are similar for an all donanemab set with modifications for the context of immunogenicity. Some results for PK/PD are from the population PK/PD analysis set. The incidence of treatment-emergent (TE) ADA in participants receiving donanemab in this integrated placebo-controlled analysis set was 812 of 922 (88.1%). In clinical studies, 88.1 % of donanemab treated patients developed anti-drug antibodies (ADA) and all of the patients with ADA had neutralising antibodies.

For the effect of immunogenicity on PK, donanemab clearance increased linearly with log(ADA titre). At the highest titre (1:5242880) observed in study AACI, median clearance increased by maximum of 39% compared with median clearance at low titre group (<1:5120; titre 1:5). This increase in clearance with titre resulted in a 17% decrease in AUCτ,ss and a 31% decrease in drug concentration before the next dose (Ctrough,ss) comparing low (<1:5120) to high (>1:20480) titre group.

Regarding effect of immunogenicity on pharmacodynamics, although donanemab exposure decreased with increasing ADA titre, the majority of participants maintained donanemab concentrations above the threshold efficacy concentration (15.2 mcg/ml) throughout the dosing interval. In a repeated-measures model of amyloid plaque reduction, each of the three donanemab maximum ADA titre categories (lower, middle, upper) show significant reduction from placebo, with some attenuation of amyloid plaque reduction in the upper category.

The incidence of treatment-emergent (TE) ADA in participants receiving donanemab in this integrated placebo-controlled analysis set was 812 of 922 (88.1%). The population PK/PD report and the ISI showed that donanemab PK was influenced by ADA titre, where donanemab serum clearance increased linearly with log (ADA titre) in the therapeutic dose range (700 to 1400 mg). Although a lower trough concentration was observed with higher ADA titre, more than 95% of participants with high titre maintained $C_{av,ss}$ above the concentration associated with reduction in amyloid plaque (15.2 µg/mL). In addition, significant amyloid plaque reduction and clinical efficacy (based on iADRS and CDR-SB) were observed irrespective of titre group, taken together, these observations do not support a need for dose adjustment.

IV.4 Clinical efficacy

The clinical efficacy data to support slowing of disease progression were based on the results of the Phase 3 confirmatory study, AACI, of which the placebo-controlled primary outcome study period has completed (AACI-PC), with supportive evidence based on the Phase 2 Study AACG.

Other studies supporting biomarker assessments included 6-month efficacy data from the ongoing active comparator Phase 3 Study AACN, and those determining dosing included in the Phase 1 Studies AACC and AACD. The Studies AACC and AACD 1b assessed the safety, tolerability, PK/PD profiles of single and multiple IV doses of donanemab.

A summary of the studies can be found in the following table.

Table 26: Summary of clinical studies.

Study Identifier; Location of Report; Report Type; Status; Participating Countries	Objective(s)	Design; Control Type	Treatment and Regimen: Dose/Route/Frequency	Treatment Duration	Number of Subjects	Diagnosis or Inclusion Criteria
Pharmacokinetic and Initial Tolerability Studies (Phase 1)						
Study I5T-MC-AACC; 5.3.3.2; Full CSR; Completed; United States and Japan	To assess safety, tolerability, and PK of single and multiple IV doses of donanemab.	Phase 1, multicenter, randomised, DB, PC, parallel-group, single-dose followed by multiple-dose, dose-escalation study.	Cohorts 1–5 (patients) received donanemab as IV infusion over at least 30 minutes of donanemab 0.1, 0.3, 1, 3, and 10 mg/kg, respectively, or placebo during the SAD phase. Doses for the same cohorts in the MAD phase included donanemab 0.3, 0.3, 1, 3, and 10 mg/kg, respectively, or placebo. Cohort 6 (patients) received donanemab 3 mg/kg	Cohorts 1–5 received a single dose in SAD phase. After a 12-week follow-up period, they received IV doses approximately once per month for up to 4 doses during	A total of 63 subjects/patients participated in this study. Of these, 12 received placebo. A total of 51 participants (45 with AD) received at least 1 dose of donanemab, and 37 patients with AD received multiple doses of donanemab.	Patients with MCI due to AD or mild-to-moderate AD. This included men or women, at least 50 years of age with evidence of memory impairment on the FCSRT-IR, an MMSE score of 16–30, no history of macrohemorrhage, and no more than 4

			as a single dose in 1 or 2 SC injections (did not participate in MAD). Cohort 7 (healthy subjects) received donanemab 1.0 mg/kg as a single-dose IV infusion over at least 30 minutes (did not participate in MAD).	the MAD phase depending on the initial doses. Cohorts 6 and 7 received only a single dose.		microhemorrhages on MRI, and a positive amyloid scan by florbetapir PET. Young healthy subjects included men aged 18 to 40 years with no more than 4 microhemorrhages on MRI.
Study I5T-MC-AACD; 5.3.3.2; Full CSR; Completed; United States and Japan	To assess safety, tolerability, PK, and PD of single and multiple IV doses of donanemab.	Phase 1b, multicenter, randomised-within-cohort, DB, PC, parallel-group, single-and multiple-dose study	Cohorts 1–3 received single doses of IV donanemab 10 mg/kg or 20 mg/kg with 72-week follow-up periods or 40 mg/kg, with 24-week follow-up period, respectively. Cohort 4 received donanemab Q2W for 24 weeks (10 mg/kg) with 48-week follow-up period. Cohorts 6 and 7 received donanemab Q4W for up to 72 weeks (10 mg/kg or 20 mg/kg, respectively) with 12-week follow-up period.	Cohorts 1–3: single doses. Cohort 4: 24 weeks. Cohorts 6–7: up to 72 weeks.	Each cohort was to include approximately 2 or 3 participants treated with placebo and 6 (single-dose) or 9 participants (multiple-dose) treated with donanemab. A total of 63 participants entered; 61 were randomly assigned, and 46 completed the study. Of the 61 randomly assigned participants, 15 received placebo and 46 received donanemab.	Patients with MCI due to AD or mild-to-moderate AD. This included men or women, at least 50 years of age with evidence of memory impairment on the FCSRT-IR, an MMSE score of 16–30, a Clinical Dementia Rating of 0.5 to 2, and a memory box score ≤ 0.5, no history of macrohemorrhage, and no more than 4 microhemorrhages on MRI, and a positive amyloid scan by florbetapir PET.
Efficacy and Safety Clinical Studies Pertinent to the Claimed Indication (Phase 2 and Phase 3)						
Study I5T-MC-AACG; 5.3.5.1; Full CSR; Completed; United States and Canada	To evaluate safety and efficacy of donanemab and assess whether removal of existing amyloid plaque can slow progression of AD over up to 72 weeks of treatment.	Phase 2, multicenter, randomised, DB, PC study.	Participants were randomly assigned to either IV donanemab 700 mg Q4W for the first 3 doses followed by IV donanemab 1400 mg Q4W for up to 72 weeks, or IV placebo Q4W for up to 72 weeks[b].	Up to 72 weeks.	A total of 272 participants were randomly assigned. Of these, 15 participants were randomly assigned to the donanemab/BACE inhibitor IV combination arm. Of the remaining 257 participants, 131 were randomly assigned to donanemab and 126 to placebo.	Patients with early symptomatic AD (prodromal AD and mild dementia due to AD) with elevated amyloid and low/medium tau burden by PET.
Study I5T-MC-AACH; Ongoing; United States and Canada	<u>Part B:</u> To provide additional safety and clinical information as an open-label study of donanemab. <u>Part C:</u> To assess the long-term effect of donanemab on PET imaging biomarkers, cognition, and function in participants who have not received IP for at least 52 weeks	Phase 2, multicenter study. <u>Part B:</u> Open-label study of donanemab in participants with symptomatic AD and naive to donanemab. <u>Part C:</u> Participants who received donanemab in the originating trial may participate in an imaging and cognitive/functional assessment visit (V 201).	<u>Part B:</u> Participants who received placebo in the originating trial receive IV donanemab 700 mg Q4W for 3 doses, followed by IV donanemab 1400 mg Q4W for up to 36 or 48 weeks. <u>Part C:</u> No donanemab infusions administered.	<u>Part B:</u> Open-label donanemab received for 36 or 48 weeks. Follow-up: up to 24 weeks. <u>Part C:</u> V 201 occurs anytime at least 52 weeks from the participant's last doubleblind visit in the originating study.	<u>Part B:</u> A total of 55 participants were included in the safety population. <u>Part C:</u> A total of 21 participants completed Part C.	Patients with symptomatic AD who have participated in a DB treatment period of a sponsor-approved originating donanemab trial (Study AACG or AACC). Participants who received donanemab in the originating study can enter Part C.

Study I5T-MC-AACI (placebo-controlled period [AACI-PC]); 5.3.5.1; Full CSR; Completed; Global Long-term extension (AACI-LTE); Ongoing; Global	AACI-PC: To assess safety, tolerability, and efficacy of donanemab in early symptomatic AD with the presence of brain pathology and to assess whether removal of existing amyloid plaque can slow progression of AD, as assessed by clinical outcomes for cognition and function. AACI-LTE: To further evaluate donanemab efficacy and safety over time.	AACI-PC: Phase 3, multicenter, randomised, DB, PC study. AACI-LTE: DB	AACI-PC: Participants who met entry criteria were randomly assigned in a 1:1 ratio to 1 of the following treatment groups: IV donanemab 700 mg Q4W for first 3 doses followed by IV donanemab 1400 mg Q4W, or placeboc. AACI-LTE Assignment in the extension period is double-blind. • Participants randomised to donanemab during the AACI-PC period who do not meet dose cessation criteria by V21 will continue receiving donanemab. ○ Participants who remained on 700 mg during the AACI-PC period will have the opportunity to dose escalate to 1400 mg at V25 or after. • Participants randomised to donanemab during the AACI-PC period who meet dose cessation criteria by V21 will be assigned to receive placebo starting at V22. • Participants randomised to placebo during the AACI-PC period will be assigned to receive donanemab starting at V22 and will follow the same dose titration as participants during the double-blind period.	AACI-PC: The treatment was up to 72 weeks. AACI-LTE: The treatment is up to 72 weeks.	AACI-PC: Approximately, 1736 participants were randomly assigned to study intervention. AACI-LTE Approximately, 1258 participants continuing to LTE, by the data cutoff date.	Patients with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain amyloid and tau pathology.
Study I5T-MC-AACI; Safety Addendum 9 (AACI-A9); Ongoing; Global	To collect open-label exposure and safety data in participants with early symptomatic AD who have proof of amyloid pathology and received donanemab.	Open-label study addendum.	Participants will receive open-label donanemab: IV donanemab 700 mg Q4W for first 3 doses followed by IV donanemab 1400 mg Q4W.	The treatment is up to 72 weeks.	A total of 1047 participants were included in the safety population.	Participants did not have to meet the flortaucipir F18 scan Inclusion Criterion (5) for this addendum
Study I5T-MC-AACN; 5.3.5.4, Ongoing; CSR synopsis; United States	To investigate amyloid plaque clearance with donanemab compared with aducanumab-avwa in participants with early symptomatic AD.	Phase 3, multicenter, randomised, open-label, active comparator study.	Participants who meet entry criteria will be randomly assigned in a 1:1 ratio to 1 of the following treatment groups: donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W, or aducanumab: refer to the package insert/routine clinical practice	The duration of treatment is up to 72 weeks.	A total of 71 participants were included in the safety population (donanemab cohort).	Patients with early symptomatic AD with elevated amyloid burden by PET.

Study AACG/I5T-MC-AACG (Phase 2): Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease.

Methods

Study AACG was a Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in patients with early symptomatic AD (prodromal AD and mild dementia due to AD) with presence of intermediate brain tau burden per flortaucipir PET. This study was conducted at 56 centres that enrolled participants in the US and Canada.

Study AACG assessed whether removal of existing amyloid plaque can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72 weeks of treatment. Dosing with donanemab started with 700 mg for 3 infusions prior to increasing to 1400 mg. Florbetapir PET scans obtained at Weeks 24 and 52 could reduce the donanemab dose from 1400 mg to 700 mg, or to placebo depending on the amyloid PET Centiloid value observed. Following the double-blind treatment period, there was a follow-up period to evaluate antidrug antibody titers for up to 48 weeks.

The study population included patients with early symptomatic AD (prodromal AD and mild dementia due to AD) with presence of intermediate brain tau burden per flortaucipir PET.

The 133-week study included a screening period of up to 9 weeks, a treatment period of up to 72 weeks with final evaluations occurring 4 weeks later at Week 76, and a 48-week immunogenicity and safety follow up period. Eighteen months is considered the minimum length for a study to be able to detect some changes in the progression of the disease in patients with prodromal/mild dementia.

Objectives

Primary:

1. To test the hypothesis that donanemab administered for up to 72 weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD.

Secondary:

1. To assess the effect of donanemab versus placebo on clinical progression in patients with early symptomatic AD.
2. To assess the effect of donanemab versus placebo on brain amyloid deposition
3. To assess the effect of donanemab versus placebo on brain tau deposition.
4. To assess the effect of donanemab versus placebo on brain volume measures.
5. To evaluate safety and tolerability of donanemab.

Treatments

Participants received 1 of the following treatments for up to 72 weeks:

- Donanemab: IV donanemab 700 mg Q4W for the first 3 doses, then 1400 mg Q4W, for up to 72 weeks. As of amendment (d), the combination therapy and oral placebo were discontinued from the study. Participants in the donanemab-C group remained blinded and were allowed to continue in the study, receiving monthly infusions of donanemab without the coadministration of the oral agent.
- Placebo: IV placebo Q4W for up to 72 weeks.
  Donanemab 700 mg or placebo administered intravenously Q4W for the first 3 doses, then donanemab 1400 mg or placebo administered intravenously Q4W for up to 72 weeks.

Subjects who met entry criteria were randomised in a 1:1 ratio to one of the above treatment arms, stratified by investigative site.

Outcomes and endpoints
Primary: Change in cognition and function as measured by the change in iADRS score from baseline to 76 weeks.

iADRS scale is a composite tool that combines scores from the AD assessment scale cognitive subscale (ADAS-Cog) and the AD Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) measuring global disease severity across the AD continuum as a single summary score.

Secondary:

1. Change from baseline to 76 weeks as measured by
    a. the change in CDR-SB score to evaluate both cognition and function
    b. the change in ADAS-Cog13 score to assess areas of cognition that are the most typically impaired in AD
    c. the change in ADCS-iADL score to assess the competence in instrumental activities of daily living
    d. the change in Mini-Mental Examination state (MMSE) score
2. Change in brain amyloid plaque deposition from baseline through 76 weeks as measured by florbetapir F18 PET scan.
3. Change in brain tau deposition from baseline to 76 weeks as measured by flortaucipir F18 PET scan.
4. Change in vMRI measures from baseline to 76 weeks.
5. Safety assessments:
    a. spontaneously reported AEs
    b. MRI (ARIA and emergent radiological findings)
    c. clinical laboratory tests
    d. vital sign and body weight measurements
    e. 12-lead ECGs
    f. physical and neurological examinations
    g. Columbia–Suicide Severity Rating Scale (C-SSRS)

In summary, the key biomarker endpoints proposed for labelling include measures that are supportive of the mechanism of action and/or important for dose decisions making, namely amyloid PET imaging, and plasma P-tau217.

To evaluate time course and sustainability of the reduction of amyloid plaque levels, the effect of donanemab versus placebo on brain amyloid deposition based on amyloid PET imaging was assessed by change in brain amyloid plaque deposition from baseline through Week 76, and percentage of participants who reached amyloid plaque clearance (defined as amyloid level <24.1 CL).

Plasma P-tau217 is a blood-based biomarker representing downstream AD pathology, is associated with both amyloid plaques and tau. An endpoint was included to assess the effect of donanemab versus placebo on P-tau217 change from baseline.

The primary and secondary endpoints were considered adequate to evaluate the effect of donanemab on beta amyloid and effect on cognitive deterioration.

Primary efficacy analysis

The null hypothesis was that there was no difference between treatment arms in the change from baseline iADRS at week 76, at a significance level of two-sided α=0.05.

The primary efficacy analysis was carried out in the FAS population. Subjects were analysed according to the treatment arm they were allocated to during randomisation irrespective of whether treatment was received or discontinued. Observations collected at unscheduled visits or off-site (by phone, video or in the participants' home) were not included in analyses. As the iADRS score is computed using ADASCog13 and ADCS-iADL, the iADRS score was considered missing if either of these two scores were missing. Total ADAS-Cog13 or ADCS-iADL scores were considered missing if >30% of items were missing. If ≤30% of items were missing, the total score was imputed.

A mixed-effects model with repeated measures (MMRM) was used to estimate the difference between treatment arms in the least-squares mean change from baseline iADRS at week 76. The MMRM treats time as a categorical variable and assumes missing data are missing at random (MAR). The following covariates were included as fixed effects: baseline iADRS score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline, and age. An unstructured covariance matrix was employed to model the covariance of within subject effect. If the MMRM model failed to converge the following tests were used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

Regarding sensitivity and supplementary analyses of the primary endpoint, the following analyses were also performed:

- Tipping point analysis to examine departures from the MAR assumption
- Bayesian Disease Progression Model (DPM) analysis to examine the difference in the rate of disease progression between treatment arms
- Random slopes analysis
- Natural cubic splines analysis
- Analysis to examine the impact of Covid-19-related treatment discontinuation
- Analysis using the PP population
- Analysis using the completers population
- Subgroup analyses

Secondary efficacy endpoints

If the primary null hypothesis was rejected, α=0.05 was propagated forward and used to test the null hypothesis for the first key secondary endpoint (CDR-SB). From here, the proportion of α allocated to other key secondary endpoints (ADAS-Cog13, iADL, MMSE) was defined using Bretz's graphical approach to ensure multiplicity control.

Missingness for ADAS-Cog13 and ADCS-iADL was handled in the same way described for the primary analysis. For CDR-SB, the total score was considered missing if >1 item was missing. If just 1 item was missing, the score was imputed. For remaining efficacy scores, if any item was missing the total score was considered missing.

For all key secondary analyses, the MMRM model was used as in the primary analysis.

Biomarker analyses

Changes from baseline in biomarkers including amyloid, tau, and vMRI were examined by treatment arm.

Changes in biomarkers at 76 weeks from baseline were examined using an MMRM model which included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as continuous effects of baseline biomarker and baseline age. The null hypothesis was that there was no difference between treatment arms in the change from baseline at week 76.

Spearman's rank correlation coefficient was calculated to compare the relationship of change at week 76 for biomarkers and clinical efficacy endpoints (iADRS, CDR-SB, ADCSi-ADL and MMSE) by treatment. Partial correlation analyses were conducted using only patients who had biomarker data at Week 76 and were adjusted for APOE4 carrier status, age and sex.

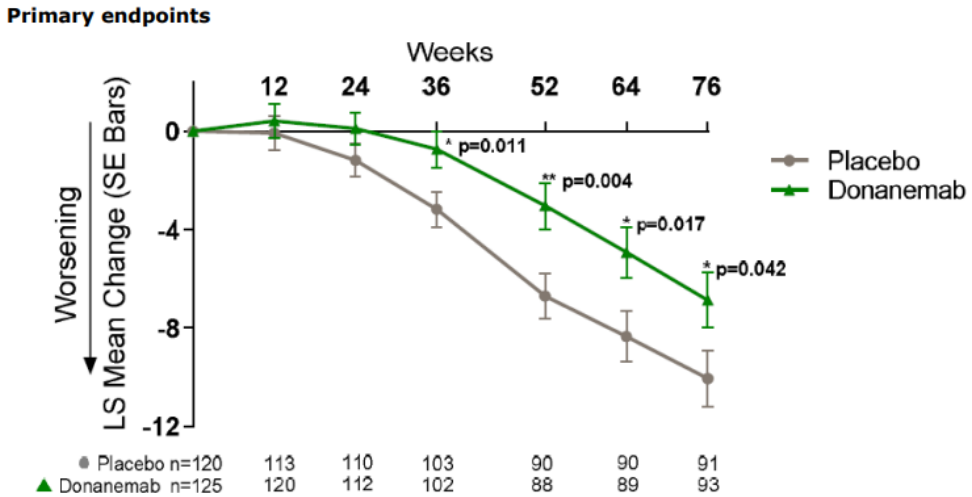
Results of primary endpoints

At Week 76, donanemab-treated participants had statistically significant less decline in cognition/function than placebo-treated participants as assessed by the **iADRS (32%** slowing, p=.04), thus meeting the primary objective of the study in the overall population. LS mean change from baseline iADRS was -10.1 for placebo and -6.9 for donanemab monotherapy (difference, 3.2; 95% CI, 0.1-6.3, p=0.042).

The primary hypothesis test was successful in demonstrating a statistically significant difference between treatment arms at the alpha level pre-specified in the protocol ($p < 0.05$).

The analysis also showed less decline in iADRS for donanemab-treated participants than placebo-treated participants at week 36, 52, and 64. Results from sensitivity analyses were consistent with the primary analysis.

Figure 50: Analysis of primary endpoints in study AACG/I5T-MC-AACG.



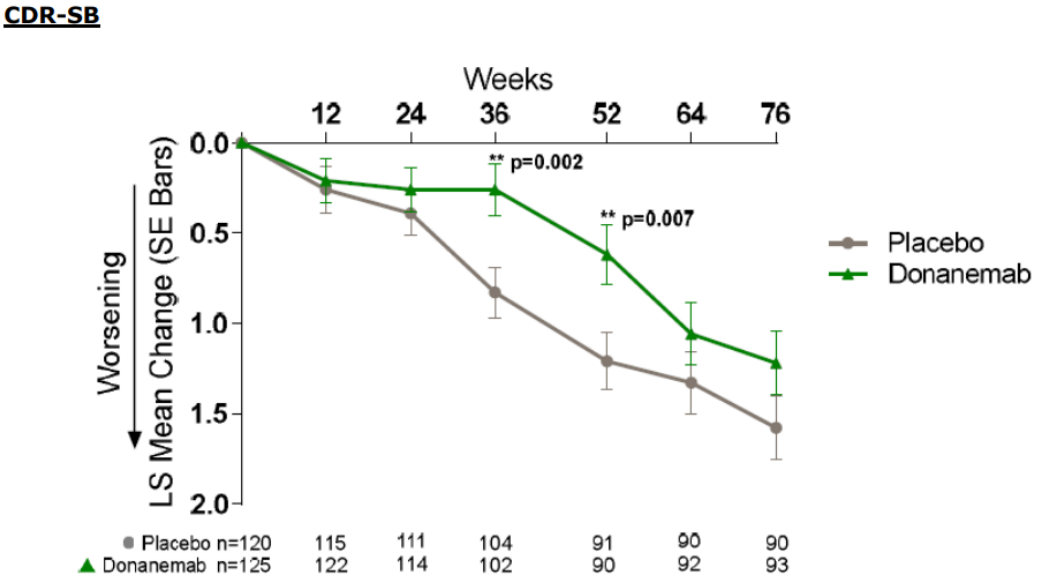
Results of secondary endpoints

Donanemab-treated participants had less decline in cognition/function over 76 weeks compared with placebo-treated participants as assessed by the **CDR-SB**; however, the

difference was not statistically significant. The key secondary hypothesis test which examined CDR-SB failed to show a significant difference between the two trial groups at week 76 the alpha level pre-specified in the protocol.

At week 76, the LS mean change for CDR-SB was 1.6 for placebo and 1.2 for donanemab (difference, -0.4; 95% CI, -0.8 to 0.1; p=0.139). The analysis suggested less decline in CDR-SB in donanemab-treated participants than placebo-treated participants at week 36 and week 52 but these were not formally tested.

Figure 51: Analysis of secondary endpoint CDR-SB in study AACG/I5T-MC-AACG.



As CDR-SB was the first key secondary endpoint in a hierarchy of secondary endpoints to be tested, and as it failed, the subsequent endpoints presented below for this study should be interpreted with caution and should not be used to draw formal conclusions. At week 76:

- donanemab-treated participants had lesser decline in cognition than placebo-treated participants as assessed by the **ADAS-Cog13** (p=.040). The analysis shows an approximately 39% reduction in cognitive decline for donanemab-treated participants compared with placebo. This was considered statistically significant. However, as described in the paragraph above, these data should be interpreted with caution.

- donanemab-treated participants had lesser decline in function than placebo-treated participants as assessed by the **ADCS-iADL**; however, the difference was not statistically significant (p=.230). The analysis shows a 23% reduction in functional decline for donanemab-treated participants compared with placebo.

- donanemab-treated participants had lesser decline in cognition than placebo-treated participants as assessed by the **MMSE**; however, the difference was not statistically significant (p=.227). The analysis shows an approximately 21% reduction in cognitive decline for donanemab-treated participants compared with placebo.

Analysis of biomarkers

At Week 76, donanemab-treated participants had statistically significantly less Aβ in the brain than placebo-treated participants as assessed by the **amyloid PET** Centiloid measurement. Slight increases in amyloid levels were observed in placebo-treated

participants.
The MMRM analysis for the amyloid PET Centiloid measurement also showed statistically significantly lesser Aβ in the brain of donanemab-treated participants than placebo-treated participants at Week 24 and Week 52.

There was not a statistically significant correlation between change from baseline to endpoint in amyloid PET biomarker values and change from baseline to endpoint in clinical efficacy scales.

The applicant carried out additional analyses to demonstrate the correlation between beta amyloid removal and clinical response to provide some evidence of an association between amyloid PET and clinical decline on iADRS and CDR-SB but also P-tau217 and GFAP. However, the beta amyloid removal and changes in the biomarkers do not seem to be directly proportional to clinical response.

All participants completing Study AACG had longitudinal tau scans at 76 weeks to measure the change in tau over the course of the study. The ANCOVA analysis showed that change from baseline to Week 76 in **global tau load**, an endpoint as determined by TauIQ method, did not differ significantly between donanemab-treated participants and placebo-treated participants, (p=.560). Additionally, an ANCOVA analysis showed no statistical difference in annualised global tau load change in donanemab-treated participants compared with placebo-treated participants (p=.600).

There was not a statistically significant correlation between change from baseline to endpoint in tau PET biomarker values (TauIQ) and change from baseline to endpoint in clinical efficacy scales.

In addition to global TauIQ load, the overall cortical tau level was also measured using MUBADA SUVr with cere-crus as reference region for SUVr calculations.

There was a statistically significant correlation between change from baseline to endpoint in **tau PET** biomarker values (MUBADA/cere-crus) and change from baseline to endpoint in the ADAS-Cog13 (r=.233, p=.037) and MMSE (r=-.225, p=.046) clinical outcomes. These significant correlations were observed in placebo-treated participants but not in donanemab treated participants.

The post hoc tau PET brain regional analyses, also used cere-crus as the reference region, and SUVr values were computed for the predefined target regions of the frontal, occipital, paretal and lateral temporal lobes.

Change in frontal lobe tau was significantly correlated with a worsening in 4 out of 5 clinical outcomes (iADRS, ADAS-Cog13, CDR-SB, and MMSE) from baseline to 76 weeks in placebo-treated participants but was not correlated in donanemab-treated participants. Donanemab had an impact on reducing regional tau accumulation in the brain, with a large impact in the frontal lobe tau accumulation. Significant slowing of the tau increases was observed across the frontal (60.8% slowing), parietal (46.3% slowing), and temporal lobes (33.1% slowing), but not occipital.

Volumetric MRI parameters were measured in 14 regions: bilateral cortical, bilateral entorhinal cortex, bilateral hippocampus, bilateral inferior parietal lobe, bilateral isthmus cingulate, bilateral lateral parietal lobe, bilateral medial temporal lobe, bilateral praecuneus, bilateral prefrontal lobe, bilateral superior temporal lobe, bilateral ventricles,

bilateral whole brain, bilateral whole temporal lobe, and bilateral white matter. Bilateral white matter hypo-intensities were also measured using T1 MRI.

In the **volumetric MRI**, statistically significant changes in brain volume were observed between treatment groups in 10 of 14 regions, although p-values are nominal and not corrected for multiplicity.

At Week 76, donanemab-treated participants had statistically significantly greater reduction in bilateral whole brain volume than placebo-treated participants. The MMRM analysis for vMRI also showed statistically significantly greater reduction in whole brain volume in donanemab-treated participants than placebo-treated participants at Week 52.
Statistically significantly greater reduction in volumes were also measured in the following regions of the brain:

- bilateral cortical – Weeks 24, 52, and 76
- bilateral isthmus cingulate – Week 52
- bilateral lateral parietal lobe – Weeks 52 and 76
- bilateral praecuneus – Weeks 24, 52, and 76
- bilateral prefrontal lobe – Weeks 52 and 76
- bilateral superior temporal lobe – Weeks 24, 52, and 76
- bilateral whole temporal lobe – Weeks 24, 52, and 76, and
- bilateral white matter – Week 76.

At Week 76, donanemab-treated participants had statistically significantly greater increase from baseline in bilateral ventricular volume than placebo-treated participants. The LS mean change difference ± SE was 2.28 ± 0.581 cm3 ($p < 0.01$). The MMRM analysis for vMRI also showed statistically significantly greater increase from baseline in bilateral ventricular volume in donanemab-treated participants than placebo-treated participants at Weeks 24 and 52.

In the MMRM analysis for vMRI, no statistically significant changes in brain volume were observed between treatment groups in 4 of 14 regions, including bilateral hippocampus.

Donanemab-treated participants had a statistically significantly greater increase from baseline volume, measured in bilateral T1 MRI white matter hypo-intensities at Weeks 24 and 76. There were no statistically significant differences found at Week 52. Mean baseline volume was also larger in the donanemab-M group compared with the placebo group.

Statistically significant changes in brain volume were observed between treatment groups in 7 of 14 regions. Statistically significantly greater annualised reduction in bilateral whole brain volume was measured in donanemab-treated participants compared with placebo-treated participants, where LS mean change difference ± SE = -2.95 ± 1.06 cm^3 (p=.006).

Statistically significantly greater annualised reduction in volumes were also measured in the following regions of the brain: bilateral cortical, bilateral praecuneus, bilateral prefrontal lobe, bilateral superior temporal lobe, and bilateral whole temporal lobe.

The ANCOVA analysis showed a statistically significantly greater annualised increase from baseline bilateral ventricular volume in donanemab-treated participants compared with placebo-treated participants, where LS mean change difference ±SE = 1.73 ±0.31 cm^3 ($p<.001$).

Correlation analyses were also performed for change from baseline to endpoint in vMRI parameters to change from baseline to endpoint in clinical outcome scales:

- Whole brain volume: In placebo-treated participants, decrease in whole brain volume correlated with worsening efficacy scores with statistically significant correlations found with all 5 clinical outcomes measures. For donanemab-treated participants, decrease in whole brain volumes correlated with worse efficacy scores for only MMSE and CDR-SB.

- Ventricles: In placebo-treated participants, increase in bilateral ventricle volume correlated with worsening efficacy scores with statistically significant correlations found with all 5 clinical outcomes measures. For donanemab-treated participants, increase in whole brain ventricle volume correlated with worse efficacy scores for iADRS and CDR-SB only.

- Hippocampus: For either placebo-treated participants or donanemab-treated participants, the change in the bilateral hippocampal volume was not significantly associated with change in ADAS-Cog13, ADCS-iADL, MMSE, iADRS, or CDR-SB.

The reduction of bilateral brain volume and increase in ventricular volume in patients treated with Donanemab was addressed by the applicant. Decreases in brain volume have been observed with other monoclonal antibodies that target amyloid. Based on the current literature the physiologic or pathologic changes that underly the observed changes in brain volume with monoclonal antibodies targeting amyloid are unclear. Several theories on the discordance between treatment effects on a cognitive scales and global brain atrophy (WBV and VV), with decreased cognitive decline being accompanied by an increase in atrophy, have been postulated. The hypothesis that brain volume changes may reflect fluid shifts or changes in morphology rather than atrophy due to neurodegeneration could be an explanation.

The MHRA agreed that the biomarker and clinical efficacy endpoints provide some reassurance and noted the clinical relevance of the observed changes in whole brain and ventricular volumes, particularly in the longer-term, were unclear.

In Donanemab treated patients, the decrease in whole brain volumes correlated with worse efficacy scores for only MMSE and CDR-SB while the increase in ventricle volume correlated with worse efficacy scores for iADRS and CDR-SB. Although, compared to placebo, only 2 of the 5 clinical outcomes were negatively affected by the changes in brain and ventricle volume.

The preplanned exploratory subgroup analyses for this study were APOE4 carrier status, clinical staging at baseline, and Tau PET level at baseline.

<u>APOE4 subgroup analysis</u>
Apolipoprotein E4 carrier status was defined as those participants with an E2/E4, E3/E4, or E4/E4 genotype; noncarrier was defined as all other genotypes. Apolipoprotein E4 carriers accounted for 73% of the entire study population

In *APOE4 carriers,* donanemab-treated participants had significantly less cognitive and functional decline compared with placebo-treated participants at week 76 on all assessment scales (iADRS, CDR-SB, ADAS-Cog13, and ADCS-iADL) except for the MMSE.

On the iADRS, donanemab-treated APOE4 carriers also showed statistically significantly less decline in cognition and function than placebo-treated APOE4 carriers at the Week 36, Week 52, and Week 64 time points.

In *APOE4 noncarriers*, donanemab treatment did not slow cognitive or functional decline compared with placebo-treated participants. Generally, in this small subgroup, donanemab treatment was not significantly worse than placebo treatment. Except for the CDR-SB 24-week time point, donanemab-treated APOE4 noncarriers did not demonstrate a reduction in cognitive or functional decline in the clinical outcome measures at any time point.

The effect of donanemab is expected to be larger in ApoE4 carriers as they have more soluble Aβ aggregate species which are toxic to synapses as compared to ApoE4 non-carriers, thus favouring more cell degeneration and death.

This seems to be confirmed by the results showing that donanemab-treated APOE4 carriers, except for the MMSE, had significantly less cognitive and functional decline on all assessment scales (iADRS, CDR-SB, ADAS-Cog13, and ADCS-iADL) compared with placebo treated APOE4 carriers at the 76-week time point. In APOE4 noncarriers there was not significant difference with placebo.

Regardless of APOE4 carrier status, donanemab-treated participants achieved a significant reduction in amyloid plaque as measured by florbetapir PET at all time points compared with placebo-treated participants ($p<.001$). Although APOE4 noncarriers had slightly higher amyloid levels at baseline, a significantly greater amyloid lowering was observed in donanemab-treated noncarriers compared with donanemab-treated APOE4 carriers at 76 weeks ($p=.013$).

Clinical staging at baseline

Clinical staging at baseline was either MCI (MMSE ≥27) or mild AD (20≤MMSE ≤ 26).

Donanemab-treated participants with mild AD had significantly less cognitive and functional decline compared with placebo-treated participants with mild AD at the 76-week endpoint (iADRS; LS mean difference, 3.99; $p=.029$). On the iADRS, donanemab-treated participants with mild AD also had significantly less cognitive and functional decline compared with placebo-treated participants with mild AD at Weeks 36, 52, and 64.

In donanemab-treated participants with mild AD, the cognitive decline was significantly lesser compared with placebo-treated participants with mild AD based on the CDR-SB assessments starting at Week 36 ($p=.028$) and extending to Week 52 ($p=.035$) but was not significant at the final time points (Week 64 or 76).

Donanemab-treated participants with MCI had significantly less cognitive and functional decline compared with placebo-treated participants with MCI at the 24-week and 52-week time points (iADRS; LSM difference, 5.97, $p=.038$). Donanemab-treated participants with MCI also had significantly less cognitive decline at Week 52 based on the CDR-SB. This small subgroup of participants with MCI treated with donanemab did not achieve statistically significantly less cognitive and functional decline at the 76- week time point on any scale.

Regardless of disease severity at baseline, donanemab-treated participants achieved a significant reduction in amyloid plaque burden as measured by florbetapir PET at all time points compared with placebo-treated participants in this subgroup. There was no difference in the change from baseline in amyloid reduction between patients with MCI and those with mild AD at any time point.

Tau-PET level at baseline

Flortaucipir PET scans were quantitatively evaluated for estimation of a tau SUVr and qualitatively for detection of a tau deposition pattern consistent with AD. Participants with an SUVr <1.10 or with a deposition pattern not consistent with AD were considered to have inadequate tau levels and were excluded from the study. The only exception to this exclusion was participants with an SUVr <1.10 but with a tau deposition pattern consistent with advanced AD. This group is referred to as "minimal tau" for the purpose of this subgroup analysis and are referred to as "no tau" in the associated statistical outputs.

Tau PET level at baseline was defined as follows using an SUVr value and visual read: minimal tau (SUVr <1.10) low tau (1.10≤SUVr <1.23), and medium tau (SUVr ≥1.23).

Collectively, these groups represent participants with intermediate tau. Participants with a tau PET SUVr >1.46 were considered to have a high tau burden and were excluded from the study.

Tau-PET sub analysis

The number of participants in the **minimal-tau** subgroup was smaller than the other subgroups.

Donanemab-treated minimal-tau participants had significantly less cognitive and functional decline than placebo-treated minimal-tau participants on the iADRS outcome measure at the 76- week time point (p=.016). The iADRS outcome was also statistically significant at Week 24. Donanemab-treated minimal-tau participants had significantly less cognitive decline compared with placebo-treated minimal-tau participants on the ADAS-Cog13 at the 76-week time point and on the iADL at Week 24.

There were no statistically significant differences observed on the CDR-SB or MMSE outcomes at any time point between donanemab-treated and placebo-treated participants.

Donanemab-treated **low-tau** participants had significantly less cognitive and functional decline than placebo-treated low-tau participants on the iADRS outcome measure at Weeks 36 and 52 (LS mean difference 4.96; p=.017). The CDR-SB supported the results of the iADRS with significantly less cognitive decline in donanemab-treated low-tau participants compared with placebo-treated low-tau participants at the same time points (36 and 52 weeks).

Donanemab-treated low-tau participants had significantly less functional decline than placebo treated low-tau participants based on the iADL subscale at Weeks 36, 52, and 64.

Except for the 12-, 64-, and 76-week time points for the MMSE, donanemab-treated **medium-tau** (SUVr ≥1.23) participants did not demonstrate a statistically significant difference in cognitive or functional decline compared with placebo-treated medium-tau participants.

Donanemab-treated participants had significantly less amyloid plaque (as measured by florbetapir PET) compared with placebo-treated participants across **all tau subgroups** ($p<0.01$).

The results from Study AACG/I5T-MC-AACG are summarised in Table 27 on the following page.

Table 27: Summary of results from Study AACG/I5T-MC-AACG.

Objectives	Endpoints	Statistical Methods	Results
Primary			
To test the hypothesis that donanemab administered for up to 72 weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD	Change in cognition and function as measured by the change in iADRS score from baseline to 76 weeks	MMRM analysis with covariate adjustments. The primary comparison is donanemab-M vs. placebo	Donanemab treatment resulted in a 32% slowing of AD progression as measured by iADRS at 76 weeks versus placebo, p=.04.
Secondary			
To assess the effect of donanemab versus placebo on clinical progression in patients with early symptomatic AD	Change from baseline to 76 weeks as measured by • the change in CDR-SB score • the change in ADAS-Cog$_{13}$ score • the change in ADCS-iADL score • the change in MMSE score	Hierarchical assessment of the secondary endpoints was performed using the Bretz's graphical approach to adjust for multiplicity; MMRM analysis with covariate adjustments.	Changes from baseline that did not meet statistical significance at 76 weeks were CDR-SB (23% slowing, p=.14), MMSE (21% slowing, p=.23), and ADCS-iADL (23% slowing, p=.23) versus placebo. Nominal statistical significance was achieved for ADAS-Cog$_{13}$. Donanemab treatment resulted in a 39% slowing of AD progression as measured by ADAS-Cog$_{13}$ at 76 weeks versus placebo, p=.04.

Objectives	Endpoints	Statistical Methods	Results
To assess the effect of donanemab versus placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through 76 weeks as measured by florbetapir F18 PET scan	At baseline, an SUVr and Centiloid value were calculated as a ratio of the composite summary region, which is an average of 6 different cortical regions (anterior cingulate, posterior cingulate, medial orbital frontal, lateral temporal, lateral parietal, precuneus), with the whole cerebellum as a reference region (SUVrCAA). An MMRM analysis was used to compare change from baseline in SUVr and Centiloid value at 76 weeks.	At Week 76, donanemab-treated participants had statistically significantly lesser amyloid beta in the brain than placebo-treated participants as assessed by the amyloid PET Centiloid measurement. The LS mean change difference ± SE was -85.06 ± 3.867, p<.001.
To assess the effect of donanemab versus placebo on brain tau deposition	Change in brain tau deposition from baseline to 76 weeks as measured by flortaucipir F18 PET scan	ANCOVA analyses of Global tau load measurements computed from TauIQ algorithm	The ANCOVA analysis showed that global tau deposition, change from baseline to Week 76, did not differ significantly between donanemab-treated participants and placebo-treated participants, where LS mean change difference (CI) was 0.01 (-0.01, 0.03), p=.560. Exploratory analyses showed significant slowing of the tau increases observed across the frontal (60.8% slowing), parietal (46.3% slowing), and temporal lobes (33.1% slowing), but not the occipital lobe.
To assess the effect of donanemab versus placebo on brain volume measures	Change in vMRI measures from baseline to 76 weeks	ANCOVA and MMRM analyses of vMRI parameters	At Week 76, donanemab-treated participants had statistically significantly greater reduction in volume in several brain regions, including bilateral whole brain volume and greater increase in bilateral ventricular volume than placebo-treated participants. No statistically significant changes were observed in bilateral hippocampal volume between groups.

Objectives	Endpoints	Statistical Methods	Results
To evaluate safety and tolerability of donanemab	Safety assessments: • spontaneously reported AEs • MRI (ARIA and emergent radiological findings) • clinical laboratory tests • vital sign and body weight measurements • 12-lead ECGs • physical and neurological examinations • Columbia–Suicide Severity Rating Scale (C-SSRS)	Multiple statistical methods were used and were dependent on the individual parameter being assessed. Safety and tolerability conclusions for donanemab also required medical interpretation of the totality of clinical evidence from this study and other studies of donanemab.	Overall incidence of deaths and participants experiencing ≥1 SAEs or ≥1 TEAEs were not significantly different in donanemab-treated participants compared with placebo. There was a significantly higher number of AEs leading to discontinuation of study treatment and study in donanemab-treated participants compared with placebo-treated participants. The most frequent TEAEs in ≥2% of participants, occurring in a statistically significantly higher proportion of donanemab-treated participants compared with placebo-treated participants, included • ARIA-E • superficial siderosis of CNS • nausea, and • IRRs. Most ARIA events reported as AE were of mild to moderate severity. The incidence of ARIA-E based on MRI was higher in the donanemab group (26.7%) compared with the placebo group (0.8%), during the double-blind period. The median time to resolution for ARIA-E in the donanemab group was 9.6 weeks. The incidence of ARIA-H based on MRI was also higher in the donanemab group (30.5%) compared with placebo (7.2%). Adverse events of nausea were significantly more frequent in the donanemab group (10.7%) compared with placebo (3.2%). Treatment-emergent adverse events of IRRs were significantly more frequent in the donanemab group (7.6%) compared with placebo (0%), and most events fully resolved on the same day as onset. There were no clinically meaningful changes in labs, vitals, or C-SSRS assessments between groups.

Abbreviations: Aβ = amyloid-β; AD = Alzheimer's disease; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADAS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living scale; AE = adverse event; ANCOVA = analysis of covariance; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema/effusion (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis); CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; CNS = central nervous system; ECG = electrocardiogram; iADRS = integrated Alzheimer's Disease Rating Scale; IRR = infusion-related reaction; LS mean= least squares mean; MMRM = Mixed Model for Repeated Measures; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; SAE = serious adverse event; SE = standard error; SUVr = Standardized Uptake Value ratio; SUVrCAA = Standardized Uptake Value ratio Cerebellum Avid Analysis; TEAE = treatment-emergent adverse event; vMRI = volumetric magnetic resonance imaging.

AACI/I5T-MC-AACI (Phase 3) Trailblazer-ALZ2: Assessment of Safety, Tolerability, and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease.

Study AACI was a multicenter, randomised, parallel-group, double-blind, placebo-controlled, Phase 3 study of donanemab to evaluate the safety and efficacy of N3pG antibody (donanemab) in patients with early symptomatic Alzheimer's disease (AD) (mild cognitive impairment and mild dementia due to AD) with the presence of brain amyloid and tau pathology over 76 weeks of the double-blind period.

The 205-week study included:

1. Lead-In: any time prior to complete screening
2. Complete Screening: up to 7 weeks
3. AACI-PC: 76 weeks
4. Extension: 78 weeks
5. Follow-Up: up to 44 weeks.

Treatments

Participants who met entry criteria were randomly assigned in a 1:1 ratio to one of these treatment groups:

- donanemab: 700 mg intravenous (IV) every 4 weeks (Q4W) for the first 3 doses and then 1400 mg IV Q4W, or
- placebo: placebo IV Q4W

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, was up to 205 weeks. The maximum duration of treatment was 150 weeks.

Participants whose amyloid plaque reduction, as measured by amyloid positron emission tomography (PET) (florbetapir F 18 or florbetaben F 18 PET) scans at Visit 8 (Week 24), Visit 15 (Week 52), Visit 21 (Week 76), Visit 28 (Week 102), or Visit 35 (Week 130), met the dose cessation criteria would have had a double-blind dose reduction of donanemab to IV placebo for the remaining duration of the study.

The AACI study included a 76-week double-blind placebo-controlled period (hereby referred to as AACI-PC) followed by a 78-week double-blind extension period. This report includes results of the AACI-PC period only.

Table 28: Study interventions administered in Study AACI.

	Product	
	Donanemab	**Placebo**
Dose (at Visits 2 to 21)	700 mg Q4W x 3 doses, and then 1400 mg Q4W for up to 72 weeks[a]	Dose N/A, Q4W for up to 72 weeks
Formulation[b]	Lyophilized powder in vial Solution in a vial	0.9% normal saline 0.9% normal saline
Route of administration	IV	IV

Abbreviations: IV = intravenous; N/A = not applicable; Q4W = every 4 weeks.

[a] Participants randomly assigned as per the original protocol, initiated treatment with 1400 mg Q4W.

[b] Most participants received solution in a vial. A total of 18 participants received lyophilized product

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study enrolled men or women, aged 60 to 85 years, inclusive,

- with gradual and progressive change in memory function reported by the participant or informant for 6 months or more
- with a Mini-Mental State Examination (MMSE) score of 20 to 28, inclusive, at Visit 601 or Visit 1
- who met flortaucipir F 18 scan criteria, and
- who met florbetapir F 18 or florbetaben F 18 scan criteria

Population was participants with early symptomatic Alzheimer's disease either with tau in the intermediate range at baseline or all randomly assigned participants including those with high tau at baseline.

Baseline demographics and clinical characteristics

The following baseline demographics were observed for all randomly assigned participants in the donanemab and placebo groups, respectively:

- had a mean age of 73.0 years in both groups.
- 57.3% and 57.4% of participants were female.
- 90.9% and 92.1% of participants were White, and
- 69.8% and 71.2% of participants were carriers of the APOE- 4.

Among randomly assigned participants in Study AACI at screening, 68% had low-medium tau levels, and 32% had high tau levels.

Objectives and endpoints

The primary objective was to assess the effect of donanemab versus placebo on clinical progression in patients with early symptomatic Alzheimer's disease.

The secondary objective was to assess the effect of donanemab versus placebo on clinical progression in patients with early symptomatic Alzheimer's disease.

The multiplicity-adjusted secondary endpoints:

1. CDR-SB change from baseline through Week 76 in at least 1 of the intermediate tau pathology population, or the overall population.
2. Change from baseline through Week 76 in at least 1 of the intermediate tau pathology population, or the overall population, as measured by
    a. ADAS-Cog13 score
    b. ADCS-iADL score, and
    c. MMSE score.
3. Change in brain amyloid plaque deposition from baseline to Week 76 as measured by florbetapir F 18 PET scan.
4. Change in brain tau deposition from baseline through Week 76 as measured by flortaucipir F 18 PET scan

The multiplicity-adjusted exploratory objectives:

1. To assess the probability of amyloid clearance in the donanemab group versus placebo
2. To assess the effect of donanemab versus placebo on time progression of the disease in participants with early symptomatic AD.
3. To assess the effect of donanemab versus placebo on the difference in hazard of progressing to first meaningful clinical worsening event.
4. To assess the effect of donanemab versus placebo on the probability of non-progression at Week 52.
5. To assess the effect of donanemab versus placebo on blood-based biomarkers

<u>Other endpoints:</u>

1. Amyloid clearance, defined as amyloid clearance value <24.1 was measured in both the intermediate tau and overall populations at Weeks 24 and 76.
2. To assess the effect of donanemab versus placebo on time progression of the disease in participants with early symptomatic AD.
3. The changes in the CDR-G, CDR-SB, and iADRS scores were considered as meeting the criteria of time to substantial decline if there were:
    a. any increase in CDR-global score from baseline
    b. 1 point or more increase in CDR-SB from baseline for participants with screening clinical status as MCI, or 2 points increase from baseline for participants with screening clinical status as mild AD, or
    c. 5 points decrease in iADRS from baseline for participants with screening clinical status as MCI, or 9 points decrease from baseline for participants with screening clinical status as mild AD. The clinical status at screening was defined as participants with mild AD (MMSE score of 20-26) and MCI (MMSE score 27-28).
4. Participants' status was classified as "no progression" if their CDR-SB change from baseline was less than or equal to 0 at 52 weeks.
5. Plasma concentration in either intermediate tau or overall population. Plasma based biomarkers included P-tau217, P-tau181b GFAP, and NfL.

<u>Statistics</u>

The primary objective of the study was examined in the sub-population with intermediate tau pathology at baseline and in the overall population.

For the primary efficacy analyses in both populations, the null hypothesis was that there was no difference between treatment arms in the least squares mean (LSM) change from baseline of iADRS score at 76 weeks. This was tested at a two-sided alpha level of 0.04 for the intermediate tau population and 0.01 for the overall population.

Each null hypothesis was tested using a natural cubic spline model with 2 degrees of freedom (NCS2). The NCS model allowed time (study visit in weeks from baseline) to be treated as a continuous variable without assuming a linear relationship with the dependent variable (iADRS score). Observations collected at unscheduled visits were not included in analyses.

As the iADRS score is computed using ADAS-Cog13 and ADCS-iADL, the iADRS score was considered missing if either of these two scores were missing. Total ADAS-Cog13 or ADCS-iADL scores were considered missing if >30% of items were missing.

Percent slowing comparing to placebo group was calculated as the LSM difference between treatment arms in change from baseline iADRS score at Week 76, divided by the LSM change from baseline iADRS for the placebo arm. A 95% confidence interval (CI) was calculated based on a Delta method.

In addition, sensitivity and supplementary analyses of the primary endpoints were conducted. These included MMRM analysis, Bayesian disease progression model (DPM) analysis, natural cubic splines with 3 degrees of freedom (NCS3), censoring at first occurrence of ARIA-E and/or IRR, treatment effect in donanemab-treated participants by ARIA-E status, Imputing iADRS score as 0 (worst) after death through week 76, completer analysis and per protocol analysis.

All secondary analyses were carried out separately for the overall population and the intermediate baseline tau population. For amyloid PET and tau PET, Spearman's rank correlation coefficient was also obtained to assess the relationship between changes in amyloid or tau levels and cognition/function (measured by iADRS, CDR-SB, ADAS-Cog13, ADCS-iADL and MMSE) from baseline through week 76.

Responder analyses included complete amyloid clearance, amyloid re-accumulation assessment after switching from donanemab to placebo and analysis of tau PET and plasma-based biomarkers by amyloid clearance status at 24 weeks.

Regarding multiplicity control, the overall type I error for primary and key secondary hypotheses was controlled at a 2-sided alpha (α) level of 0.05. Primary hypothesis testing in the intermediate tau population was allocated α=0.04 and primary hypothesis testing in the overall population was allocated α=0.01. If either primary hypothesis was rejected, the allocated α was recycled for the testing of key secondary hypotheses using specified weights.

Summary of the design and conduct

The primary endpoint was the change in iADRS at 76 weeks from baseline in the intermediate baseline tau population and the overall population. Secondary endpoints included CDR-SB, ADAS-Cog13, iADL, MMSE, amyloid PET, tau PET and vMRI.

Primary analyses were carried out using a natural cubic spline model with supplementary analyses carried out using other models, such as MMRM, to assess robustness. The null hypothesis of no difference between treatment arms was tested at a two-sided alpha level of 0.04 for the intermediate population and 0.01 for the overall population, ensuring appropriate control of type I error.

Treatment discontinuation as well as initiation of or changes in standard-of-care medication were considered intercurrent events and a treatment policy strategy was followed which is considered appropriate for the primary analysis.

Participant disposition

Of the over 8000 participants assessed for eligibility, 78.9% were screen failures. The screen failure rate was stated to reflect the broad net that participating sites cast in recruiting potential study participants and did not reflect a lack of generalisability from the study population to the target population for clinical use. Nearly 70% of the screen failures relate to factors that identify patients who do not have early symptomatic AD.

69.8% of the donanemab group and 71.2% of the placebo group of participants were carriers of the APOE-Ɛ4.

In total, 874 participants received placebo and 853 received donanemab. A higher proportion of participants in the donanemab arm discontinued from the study compared with the placebo arm (26.9% vs 19.7%). This was primarily driven by larger numbers in the donanemab arm discontinuing due to adverse events, and withdrawal due to decisions by the participant or physician.

Primary efficacy results

Figure 52: Analysis of change from baseline on iADRS, Study AACI-PC Low/Medium Tau Population (NCS2).

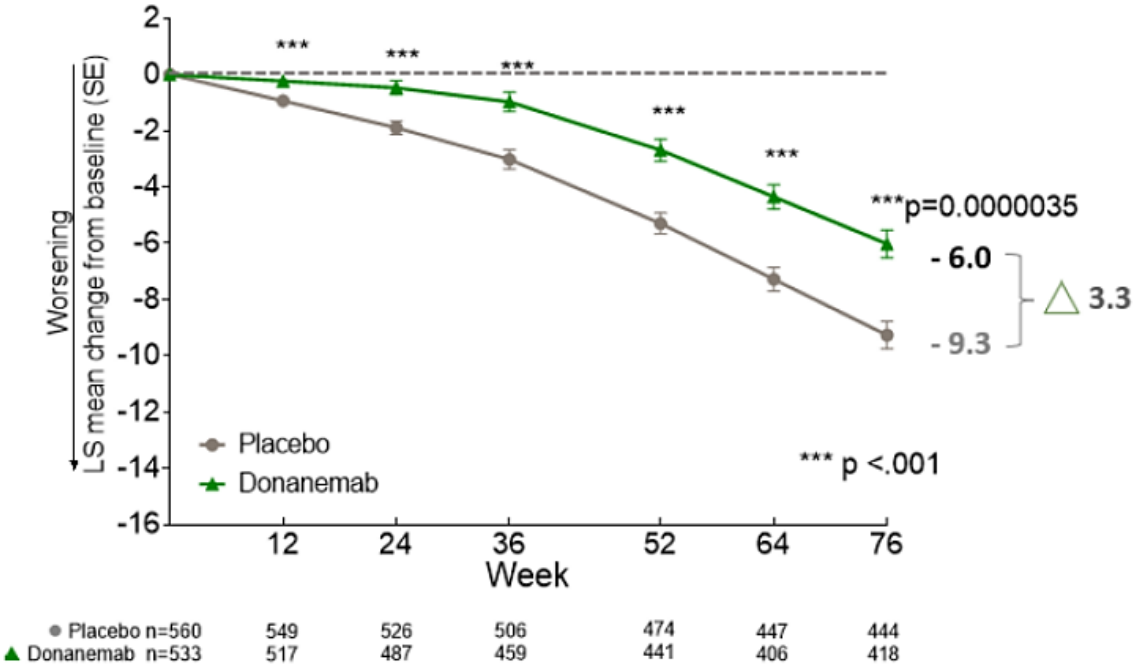


Table 29: Primary and sensitivity analyses comparing change from baseline iADRS at 76 weeks in placebo-treated (PBO) and donanemab-treated (DON) subjects.

Analysis	Intermediate baseline tau population			Overall population		
	LS Mean change from baseline iADRS (PBO vs. DON)	Difference in mean change (95% CI) (DON - PBO)	% Slowing of deterioration on iARDS scale (95% CI)	LS Mean change from baseline iADRS (PBO vs. DON)	Difference in mean change (95% CI) (DON - PBO)	% Slowing of deterioration on iARDS scale (95% CI)
NCS2 (**Primary**)	-9.3 vs -6.0	3.3 (1.9, 4.6)[2]	35.1 (19.9, 50.2)	-13.1 vs -10.2	2.9 (1.5, 4.3)[2]	22.3 (11.4, 33.2)
MMRM	-9.6 vs -5.8	3.8 (2.4, 5.3)	39.6 (Not given)	-13.2 vs -10.2	3.0 (1.6, 4.5)	22.9 (Not given)
Bayesian DPM	-8.7 vs -5.8	2.9 (2.1, 3.8)	34.0 (25.1, 41.5)	-11.9 vs -8.9	3.0 (2.2, 3.8)	25.0 (19.4, 31.0)
NCS3	-9.3 vs -5.7	3.7 (2.2, 5.1)	39.1 (23.4, 54.9)	-13.0 vs -10.0	3.1 (1.6, 4.5)	23.7 (12.4, 34.9)
Data censored after ARIA-E/IRR[1]	-9.3 vs -6.2	3.1 (1.6, 4.6)	33.4 (16.6, 50.2)	-13.1 vs -11.0	2.1 (0.5, 3.7)	16.0 (3.7, 28.3)
PBO vs. DON with ARIA-E[1]	-9.3 vs -5.7	3.6 (1.4, 5.8)	39.1 (15.1, 63.1)	-13.1 vs -8.2	4.9 (2.7, 7.2)	37.7 (20.3, 55.1)
PBO vs DON without ARIA-E[1]	-9.3 vs -6.1	3.1 (1.7, 4.6)	33.8 (17.5, 50.1)	-13.1 vs -10.9	2.2 (0.7, 3.8)	17.1 (5.4, 28.9)
iADRS=0 for subjects who died[1]	-10.0 vs -6.8	3.2 (1.3, 5.0)	31.6 (12.2, 51.0)	-13.7 vs -10.8	2.9 (1.1, 4.6)	21.0 (8.1, 33.9)
Per-Protocol[1]	-8.2 vs -5.3	2.9 (1.2, 4.5)	35.0 (14.5, 55.6)	-10.7 vs -7.7	2.9 (1.2, 4.6)	27.4 (11.4, 43.3)
Completers[1]	-8.1 vs -5.3	2.8 (1.5, 4.2)	34.5 (17.6, 51.5)	-11.6 vs -8.8	2.8 (1.4, 4.2)	23.9 (12.0, 35.9)

[1]Used NCS2 model, [2]P<0.001.

In the intermediate baseline tau population, the mean change from baseline iADRS score at 76 weeks was −9.3 for placebo and −6.0 for donanemab (difference, 3.3; 95% CI, 1.9-4.6; p<0.001). This was reported as a 35.1% (95% CI, 19.9-50.2%) slowing of deterioration on the iADRS scale. Results were robust across sensitivity analyses. A subsequent secondary analysis estimated the slowing in the donanemab treatment arm corresponded to a delay in progression of 4.4 months (95% CI, 1.9-6.9) on the iADRS scale.

In the overall population (which included subjects with high baseline tau), the mean change from baseline iADRS score at 76 weeks was −13.1 for placebo and −10.2 for donanemab (difference, 2.9; 95% CI, 1.5-4.3; p<0.001). This was reported as a 22.3% (95% CI, 11.4-33.2%) slowing of deterioration on the iADRS scale. Results were robust across sensitivity analyses. A subsequent secondary analysis estimated the slowing in the donanemab treatment arm corresponded to a delay in progression of 1.4 months (95% CI, 0.5-2.3) on the iADRS scale.

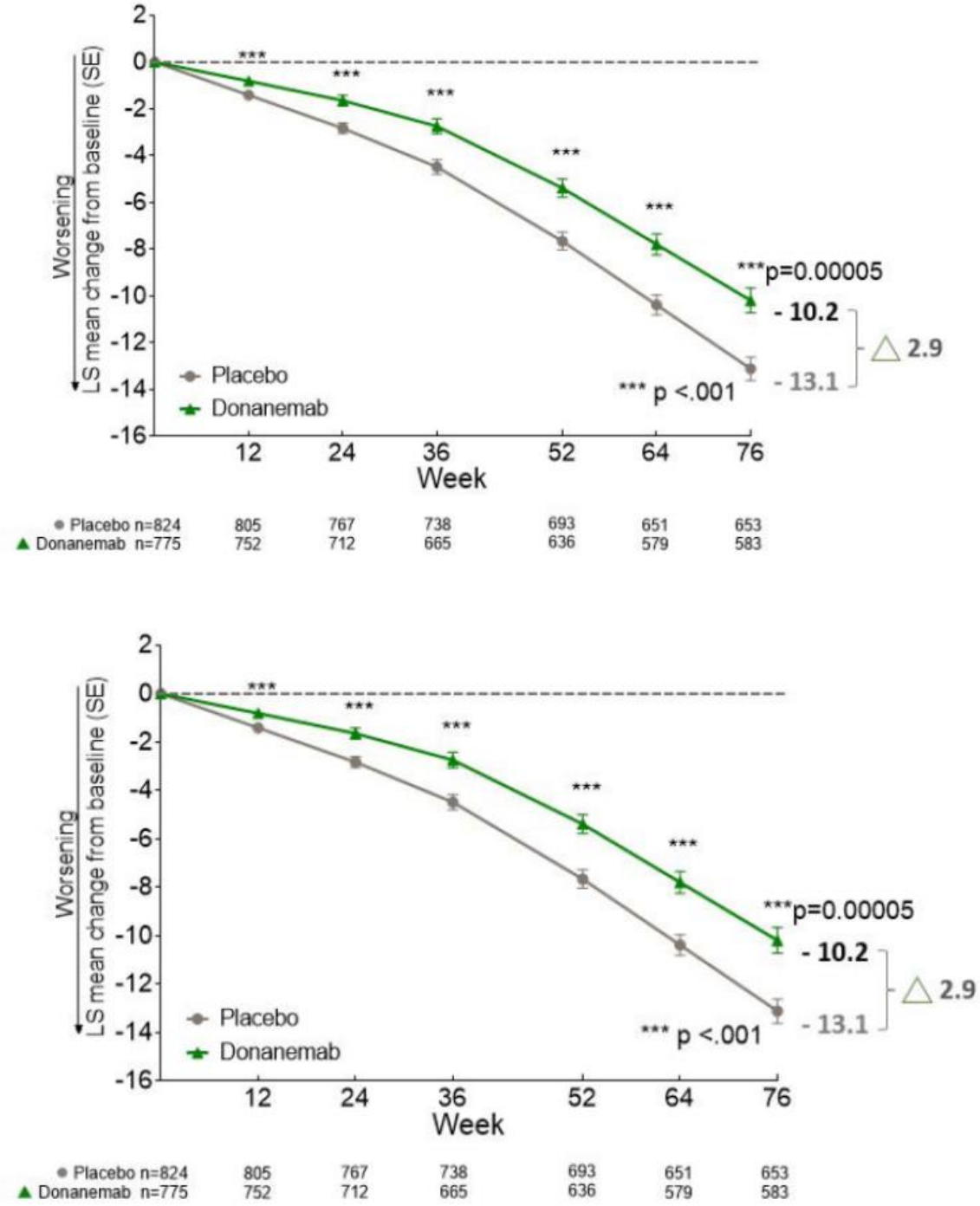
Observations from unscheduled visits comprised <1% of all collected iADRS data.
The applicant repeated the primary analyses of iADRS in the intermediate and overall populations and included data from unscheduled visits. After including data from unscheduled visits, the treatment difference in the intermediate population was 3.3 (95% CI, 1.9 to 4.6) and the treatment difference in the overall population was 3.0 (95% CI, 1.6 to 4.4). Results were consistent with the main analysis.

Primary hypothesis tests in the intermediate and overall populations were therefore successful in demonstrating a statistically significant difference between treatment arms in change from baseline iADRS score at 76 weeks (at the alpha levels pre-specified in the protocol, p<0.01 and p<0.01, respectively**).**

Whilst donanemab has a clear impact on amyloid beta plaque, and the results of the primary and key secondary efficacy endpoints were statistically significant, it remains to be established whether this reduction in amyloid beta plaque results in a clinically meaningful benefit for patients with early Alzheimer's disease.

Analyses were repeated using conservative methods (jump-to-reference imputation) for the handling of missing data and led to a reduction between treatment arms in the difference in mean change, the percentage less decline/progression, and the time-saved in months. Despite a reduction in effect size, results favoured donanemab and demonstrated the robustness of findings from main analyses. For the primary endpoint (iADRS), the difference in mean change from placebo in the combined population was 1.75 (95 % CI, 0.38 to 3.13) and in the low-medium tau population was 2.22 (95 % CI, 0.87 to 3.57).

Figure 53: NCS2: iADRS13 change from baseline by treatment, overall population (AACI-PC period).



At Week 76, donanemab-treated participants had statistically significantly less clinical progression compared with the placebo-treated participants as assessed by the iADRS change from baseline values in the overall population.

A statistically significant slowing of 22% as measured by the iADRS, in the combined population at Week 76, equated to 1.4 months delay in disease progression, and 30% lower risk of progressing to a later stage of disease, with substantial decline observed in 29% of donanemab-treated participants and 40% of placebo-treated participants.

At Week 76 donanemab-treated participants had statistically significantly less clinical progression compared with placebo-treated participants as assessed by the iADRS change from baseline values in the intermediate tau population (35% slowing of clinical progression = 4.4 months of delay in disease progression) in donanemab-treated participants compared with placebo-treated participants. The difference in LS mean change value ± SE was 2.92 ± 0.72 ($p<0.001$).

The NCS2 analysis also showed significant differences in clinical progression in donanemab-treated participants compared with placebo-treated participants at all prespecified time points of Weeks 24, 36, 52, and 64 (nominal $p<0.001$) in the overall population.

Significant differences in clinical progression were observed in donanemab-treated participants compared with placebo-treated participants at

- Weeks 36, 52, 64, and 76 for the PP analyses set (nominal p-values of .04, .005, and .001, respectively), and
- Weeks 12, 24, 36, 52, 64, and 76 (nominal $p<0.01$) for the completer analyses set.

Secondary Efficacy and Biomarker Endpoints

Secondary efficacy endpoints included CDR-SB, ADAS-Cog13, iADL, and MMSE and results are summarised in Table 30.

- **CDR-SB**
  At Week 76, donanemab-treated participants had less clinical progression compared with placebo-treated participants as assessed by the CDR-SB change from baseline values in the intermediate tau population (36% slowing of clinical progression) and overall population (29% slowing of clinical progression).

- **ADAS-Cog13**
  At Week 76, donanemab-treated participants had statistically significantly less decline in cognition compared with placebo-treated participants as assessed by the ADAS-Cog13 change from baseline values in the intermediate tau population (32% slowing of clinical progression) and in the overall population (20% slowing of clinical progression) in donanemab-treated participants compared with placebo-treated participants.

- **ADCS-iADL**
  At Week 76, donanemab-treated participants had statistically significantly less decline in clinical in the intermediate tau population (40% slowing of clinical progression) in donanemab-treated participants compared with placebo-treated participants and in the overall population (28% slowing of clinical progression) in donanemab treated participants compared with placebo-treated participants.

- **MMSE**
  At Week 76, donanemab-treated participants had less decline in cognition than placebo-treated participants as assessed by the MMSE change from baseline values in the intermediate tau population. (23% slowing of clinical progression) and in the overall population (16% slowing of clinical progression) in donanemab-treated participants compared with placebo-treated participants.

  The differences in response based on the tau range at baseline is further confirmed by the results from the Phase 2 study (AACG) where donanemab-treated medium-tau (SUVr >1.23) participants did not demonstrate a statistically significant difference in cognitive or functional decline compared with placebo-treated medium-tau participants suggesting that when the Tau burden is > 1.23, the difference with placebo is not statistically significant.

  In the phase 3 study (AACI) statistically significant difference vs placebo was observed for the low-medium TAU population.

In both the intermediate tau and overall population at week 76, the donanemab group showed less progression than the placebo group for each of these endpoints (see Table 30). For CDR-SB and MMSE, the difference between treatment arms at week 76 was approximately 0.5-1 point whereas for ADAS-Cog13 and iADL the difference was 1-2 points. Differences between treatment groups were observed from week 12 onwards across the endpoints

The time saved (in months) due to less progression in the donanemab arm compared with the placebo arm was estimated for iADRS, CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE (see Table 31). Time saved ranged from 1.4 – 7.5 months across the different endpoints.

Biomarker endpoints included amyloid PET, tau PET, plasma P-tau217, plasma P-tau181, plasma GFAP, and plasma NfL.

In both the intermediate tau and overall populations, amyloid plaque was markedly reduced at 76 weeks from baseline in donanemab-treated subjects compared with placebo-treated subjects. A reduction in amyloid plaque was also observed at weeks 24 and 52. Conversely, there was no evidence of a difference in tau PET between treatment arms at 76 weeks.

Plasma-based p-tau217, p-tau181 and GFAP appeared reduced in donanemab-treated participants and increased in placebo-treated participants at week 76. Plasma-based NfL levels increased from baseline in both donanemab and placebo groups.

Similar decrease in the P-tau217 level in the donanemab group and increase in the placebo group were observed for overall population at Weeks 24 and 76 (p<.0001).

In the intermediate tau population:

- change from baseline plasma P-tau217 level was statistically significantly reduced in donanemab-treated participants and increased in placebo-treated participants at Weeks 24 and 76 (p<.0001).
- plasma GFAP level was reduced in donanemab-treated participants and increased in placebo-treated participants at Weeks 24 and 76 (nominal p<.001).
- plasma P-tau181 level was reduced in donanemab-treated participants and increased in placebo-treated participants at Weeks 24 and 76 (p<.0001)

NfL level increased from baseline in the placebo- and donanemab-treated groups in both intermediate and overall populations at Weeks 24 and 76.

In the intermediate tau population, the ANCOVA showed that change from baseline to Week 76 in frontal tau deposition (frontal SUVr) did not differ significantly in the donanemab group compared with the placebo group (p=.97). Similar trends were observed in the overall population (p=.45)

For the volumetric MRI endpoint, in both the intermediate tau and overall populations, the vMRI at Week 76 showed a greater decrease in the whole brain volume (nominal p<001) and a greater increase in ventricular volume (nominal p<0.01) in donanemab-treated participants compared with placebo-treated participants. A lesser decrease in the hippocampal volume was observed in donanemab-treated participants compared with placebo-treated patients

Table 30: Secondary analyses and sensitivity analyses examining changes from baseline at 76 weeks in placebo-treated (PBO) and donanemab-treated (DON) subjects.

	Intermediate baseline tau population			**Overall population**		
Analysis	LS Mean change from baseline score (PBO vs. DON)	Difference in mean change (95% CI) (DON - PBO)	% Slowing of deterioration (95% CI)	LS Mean change from baseline score (PBO vs. DON)	Difference in mean change (95% CI) (DON - PBO)	% Slowing of deterioration (95% CI)
CDR-SB						
MMRM*	1.9 vs 1.2	-0.7 (-1.0, -0.4)	36.0 (Not given)	2.4 vs 1.7	-0.7 (-1.0, -0.5)	28.9 (Not given)
NCS2	1.8 vs 1.2	-0.7 (-0.9, -0.4)	37.0 (22.3, 51.8)	2.3 vs 1.7	-0.7 (-0.9, -0.4)	28.9 (18.3, 39.5)
Bayesian DPM	1.8 vs 1.1	-0.7 (-0.8, -0.5)	38.0 (30.6, 45.3)	2.2 vs 1.6	-0.7 (-0.8, -0.5)	30.0 (24.4, 35.2)
NCS3	1.8 vs 1.2	-0.7 (-0.9, -0.4)	36.4 (21.3-51.5)	2.3 vs 1.7	-0.7 (-0.9, -0.4)	29.0 (18.1, 39.8)
PBO vs. DON with ARIA-E, NCS2	1.8 vs 0.8	-1.1 (-1.5, -0.6)	57.3 (33.5, 81.0)	2.3 vs 1.2	-1.1 (-1.5, -0.7)	47.2 (29.9, 64.4)
PBO vs DON without ARIA-E, NCS2	1.8 vs 1.3	-0.6 (-0.8, -0.3)	30.6 (14.9, 46.3)	2.3 vs 1.8	-0.5 (-0.8, -0.3)	23.1 (11.7, 34.5)
ADAS-Cog13						
NCS2*	4.7 vs 3.2	-1.5 (-2.3, -0.8)	32.4 (16.6, 48.4)	6.8 vs 5.5	-1.3 (-2.1, -0.6)	19.5 (8.2, 30.8)
MMRM	4.9 vs 3.2	-1.7 (-2.5, -0.9)	35.3 (Not given)	7.1 vs 5.7	-1.4 (-2.1, -0.6)	19.2 (Not given)
iADL						
NCS2*	-4.6 vs -2.8	1.8 (0.9, 2.7)	39.9 (19.2, 60.6)	-6.1 vs -4.4	1.7 (0.8, 2.6)	27.8 (13.5, 42.1)
MMRM	-4.7 vs -2.7	2.0 (1.0, 3.0)	42.9 (Not given)	-6.3 vs -4.6	1.8 (0.9, 2.6)	27.7 (Not given)
MMSE						
NCS2	-2.1 vs -1.6	0.5 (0.1, 0.9)	22.9 (4.0, 41.8)	-2.9 vs -2.5	0.5 (0.1, 0.8)	16.1 (3.5, 28.7)
MMRM	-2.2 vs -1.6	0.6 (0.1, 1.0)	26.4 (Not given)	-3.2 vs -2.8	0.5 (0.1, 0.9)	14.8 (Not given)
Amyloid Centiloid PET						
MMRM*	0.2 vs -88.0	-88.2 (-91.2, -85.2)	Not given	-0.7 vs -87.0	-86.4 (-88.9, -83.9)	Not given
Tau SUVr PET						
Frontal Lobe, ANCOVA**	0.03 vs 0.03	0.0002 (-0.01, 0.01)	Not given	0.04 vs 0.04	-0.004 (-0.01, 0.01)	Not given
MUBADA, ANCOVA	0.07 vs 0.07	-0.002 (-0.02, 0.01)	Not given	0.07 vs 0.06	-0.01 (-0.02, 0.01)	Not given
Plasma P-tau217						
MMRM*	0.04 vs -0.2	-0.3 (-0.3, -0.2)	Not given	0.03 vs -0.2	-0.2 (-0.2, -0.2)	Not given
Plasma P-tau181						
MMRM	0.01 vs -0.09	-0.1 (-0.1, -0.09)	Not given	0.02 vs -0.08	-0.11 (-0.12, -0.10)	Not given
Plasma G-FAP						
MMRM	0.04 vs -0.1	-0.1 (-0.2, -0.1)	Not given	0.1 vs -0.1	-0.1 (-0.2, -0.1)	Not given
Plasma NfL						
MMRM	0.05 vs 0.03	-0.01 (-0.03, 0.01)	Not given	0.05 vs 0.05	-0.01 (-0.02, 0.01)	Not given
vMRI						
Bilateral hippocampus, MMRM	-0.2 vs -0.2	0.02 (-0.00, 0.03)	6.8 (Not given)	-0.2 vs -0.2	0.02 (0.01, 0.04)	9.7 (Not given)
Bilateral whole brain, MMRM	-18.0 vs -24.3	-6.3 (-7.6, -5.1)	-35.3 (Not given)	-20.8 vs -27.5	-6.7 (-7.8, -5.6)	-32.0 (Not given)
Bilateral ventricles, MMRM	6.1 vs 8.5	2.4 (1.9, 2.9)	-39.5 (Not given)	7.1 vs 10.1	3.0 (2.5, 3.5)	-42.9 (Not given)

*Tested at α level pre-specified in the strategy for multiplicity control and was successful in demonstrating statistical significance, **The intermediate tau population was tested at the α level pre-specified in strategy for multiplicity control and did not demonstrate statistical significance.

Table 31: Time saved on iADRS, CDR-SB, ADAS-Cog13, iADL and MMSE scales at 18 months.

	Intermediate baseline tau population		**Overall population**	
	Time saved in months (95% CI)	% Time saved (95% CI)	Time saved in months (95% CI)	% Time saved (95% CI)
iADRS*	4.4 (1.9, 6.9)	24.9 (10.7, 39.1)	1.4 (0.5, 2.3)	7.9 (2.6, 13.1)
CDR-SB*	7.5 (5.7, 9.4)	42.9 (32.4, 53.4)	5.4 (3.9, 7.0)	31.0 (22.2, 39.8)
ADAS-Cog13	3.1 (-0.05, 6.3)	17.7 (-0.3, 35.6)	1.8 (0.6, 2.9)	10.1 (3.5, 16.7)
iADL	4.1 (2.4, 5.8	23.4 (13.5, 33.3)	3.6 (2.0, 5.2)	20.4 (11.5, 29.4)
MMSE	1.7 (-0.2, 3.5)	9.4 (-0.9, 19.7)	5.4 (3.9, 7.0)	31.0 (22.2, 39.8)
*Tested at α level pre-specified in the strategy for multiplicity control and was successful in demonstrating statistical significance				

Dose cessation, amyloid clearance and assessment of amyloid plaque re-accumulation
At week 24, approximately 20% of participants in the intermediate tau population and 17% of participants in the overall population showed a significant reduction in amyloid plaque and met dose cessation criteria. Among these participants, amyloid plaque levels at Weeks 24, 52, and 76 were very close to each other and did not suggest marked re-accumulation.

A total of 34% in the intermediate tau population and 30% donanemab-treated participants in the overall population had amyloid clearance defined as an amyloid plaque level of less than 24.1 CL at as early as Week 24 (p<.0001).

At week 52, approximately 52% of participants in the intermediate tau population and 47% of participants in the overall population showed a significant reduction in amyloid plaque and met dose cessation criteria. Among these participants, amyloid plaque levels at Weeks 52 and 76 were very close to each other and did not suggest marked re-accumulation.

The patients who met the cessation criteria at weeks 24 and 52 didn't seem to have a marked re-accumulation of amyloid plaques at week 76.

At Week 76, statistically significant results in amyloid clearance were observed in donanemab-treated participants compared with placebo-treated participants in both intermediate tau and overall populations (p<.0001). Approximately 74% participants in the intermediate tau population and 69% participants in the overall population showed a significant reduction in amyloid plaque and met the dose cessation criteria.

APOE-ε4 carrier status
Study AACI demonstrated that donanemab treatment showed slowing of clinical decline across APOE-Ɛ4carrier and noncarrier subgroups, as measured across all clinical efficacy scales.

Donanemab treatment in both carriers and non-carriers was associated with less decline on iADRS and CDR-SB scores and a significant reduction in amyloid plaque compared with placebo. This is consistent with previous data from phase 2 for carriers but not for non-carriers which previously were not seen to benefit.

APOE-Ɛ4 carrier status was further categorised into heterozygous carrier (Ɛ2/ Ɛ4, Ɛ3/ Ɛ4) and homozygous carrier (Ɛ4/ Ɛ4), for APOE-Ɛ4 genotype subgroup analyses with noncarriers. Slowing of clinical decline was observed across heterozygous and homozygous carrier subgroups.

However, among carriers, the reduced decline in iADRS and CDR-SB was driven by those with one E4 allele. Those with two E4 alleles did not demonstrate a significant slowing in decline. This was concerning, as this subgroup are at greater risk with donanemab treatment due to a higher incidence of ARIA (including symptomatic and serious ARIA) compared with heterozygotes and non-carriers. Whilst it is acknowledged that homozygous subjects are one of the smaller subgroups tested, these findings raised significant concerns about the benefit in these subjects and the benefit/risk given their higher risk with treatment.

Reduction in amyloid plaque was observed regardless of E4 allele number although the reduction was smaller among those with two E4 alleles.

Donanemab treatment did not result in a significant reduction in tau in either carriers or non-carriers compared with placebo. These factors had not previously been explored in the Phase II study.

Table 32: Change from baselines at 76 weeks for iADRS, CDR-SB, Amyloid PET and Tau SUVr in placebo-treated (PBO) and donanemab-treated (DON) subjected, by carrier status and number of E4 alleles.

	Intermediate baseline tau population		Overall population	
	LS Mean change from baseline score (PBO vs. DON)	Difference in mean change (95% CI)* (DON - PBO)	LS Mean change from baseline score (PBO vs. DON)	Difference in mean change (95% CI)* (DON – PBO)
i-ADRS				
Non-carriers	-11.7 vs -7.6	4.0 (1.4, 6.6)	-16.3 vs -11.7	4.6 (2.0, 7.1)
All carriers	-8.4 vs -5.4	3.0 (1.4, 4.6)	-11.8 vs -9.4	2.4 (0.8, 4.1)
Carrier, 1 allele	-9.0 vs -5.7	3.4 (1.6, 5.2)	-12.1 vs -9.2	2.9 (1.0, 4.8)
Carrier, 2 alleles	-6.3 vs -4.4	1.9 (-1.4, 5.3)	-10.9 vs -9.9	1.0 (-2.4, 4.4)
CDR-SB				
Non-carrier	2.1 vs 1.3	-0.8 (-1.3, -0.3)	2.6 vs 1.9	-0.8 (-1.2, -0.3)
All carriers	1.7 vs 1.1	-0.6 (-0.9, -0.3)	2.2 vs 1.6	-0.7 (-0.9, -0.4)
Carrier, 1 allele	1.7 vs 1.0	-0.8 (-1.1, -0.4)	2.2 vs 1.4	-0.7 (-1.1, -0.4)
Carrier, 2 alleles	1.7 vs 1.5	-0.2 (-0.8, 0.4)	2.3 vs 1.9	-0.4 (-1.0, 0.2)
Amyloid Centiloid PET				
Non-carrier	2.0 vs -94.1	-96.1 (-101.5, -90.7)	0.4 vs -93.6	-94.0 (-98.4, -89.6)
All carriers	-0.4 vs -85.8	-85.4 (-89.0, -81.8)	-1.0 vs -84.2	-83.2 (-86.1, -80.2)
Carrier, 1 allele	-0.01 vs -88.3	-88.4 (-92.4, -84.3)	-0.8 vs -87.5	-86.7 (-90.1, -83.3)
Carrier, 2 alleles	-1.8 vs -76.5	-74.8 (-81.8, -67.7)	-1.7 vs -73.4	-71.7 (-77.6, -65.8)
Tau SUVr PET, MUBADA				
Non-carrier	0.06 vs 0.06	-0.001 (0.01)	0.05 vs 0.05	-0.01 (0.01)
All carriers	0.08 vs 0.07	-0.001 (0.01)	0.08 vs 0.07	-0.005 (0.01)
Carrier, 1 allele	0.07 vs 0.07	0.001 (0.01)	0.08 vs 0.07	-0.004 (0.01)
Carrier, 2 alleles	0.09 vs 0.08	-0.01 (0.02)	0.08 vs 0.07	-0.01 (0.02)
Tau SUVr PET, Frontal Lobe				
Non-carrier	0.02 vs 0.02	0.003 (0.01)	0.04 vs 0.04	-0.003 (0.01)
All carriers	0.03 vs 0.03	-0.001 (0.01)	0.06 vs 0.05	-0.004 (0.01)
Carrier, 1 allele	0.03 vs 0.03	-0.0001 (0.01)	0.05 vs 0.05	-0.005 (0.01)
Carrier, 2 alleles	0.04 vs 0.04	-0.0004 (0.01)	0.06 vs 0.06	-0.0001 (0.01)

*Standard error used for Tau analyses instead of 95% CI

Phase 3 study I5T-MC-AACN (Trailblazer-ALZ-4)

Study I5T-MC-AACN (AACN) was an ongoing Phase 3, open-label, active comparator study to evaluate the superiority of donanemab to aducanumab in participants with early symptomatic Alzheimer's disease.

The MHRA noted the study demonstrated the superiority of donanemab over aducanumab in the ability to clear amyloid plaques. Clinical benefit correlated to amyloid plaque reduction was not assessed. Therefore, these results do not provide any information on the clinical benefit of donanemab. Furthermore, at the time of this application, aducanumab was not approved in the UK or any EU countries. As such, the MHRA considered the results of this study of little relevance.

Overall conclusions on clinical efficacy

Donanemab has demonstrated statistically significant difference compared to placebo in the primary endpoint in both the phase 2 (AACG) and Phase 3 (AACI) clinical studies

In the Phase 2 study (AACG), at week 76, donanemab-treated participants had statistically significantly less decline in cognition/function than placebo-treated participants as assessed by the primary endpoint, iADRS (32% slowing, p=.04). The key secondary hypothesis test examined change in CDR-SB at 76 weeks from baseline. At week 76, the LS mean change for CDR-SB was 1.6 for placebo and 1.2 for donanemab (difference, -0.4; 95% CI, -0.8 to 0.1; p=0.139). Although donanemab-treated subjects had less decline from baseline compared with placebo-treated subjects, the difference between treatment arms was not statistically significant at the alpha level pre-specified in the protocol. The analysis suggested less decline in CDR-SB in donanemab-treated participants than placebo-treated participants at week 36 and week 52 but these were not formally tested. Trends suggesting less decline at 76 weeks from baseline among donanemab-treated participants were also observed for ADAS-Cog13, iADL and MMSE. However, as CDR-SB was the first key secondary endpoint in the hierarchy of secondary endpoints to be tested, and as it failed, results relating to the subsequent key secondary endpoints in the phase 2 study should be interpreted with caution.

In the Phase 3 study (AACI), at week 76, donanemab-treated participants had statistically significantly less clinical progression compared with placebo-treated participants as assessed by the iADRS change from baseline values in the low-medium intermediate tau population (35% slowing of clinical progression= 4.4 months of delay in disease progression) and overall population (22% slowing of clinical progression= 1.4 month of delay in disease progression).

Based on the sub population analysis conducted by the applicant, the ability to slow clinical progression seems to be influenced by some characteristics such as the APOE carrier status and the TAU levels at baseline.

In the Phase 3 study, donanemab treatment in both carriers and non-carriers was associated with less decline on iADRS and CDR-SB scores and a significant reduction in amyloid plaque compared with placebo. However, among carriers, the reduced decline in iADRS and CDR-SB was largely driven by those with one E4 allele. Those with two E4 alleles did not demonstrate a statistically significant slowing in decline although the point estimate was trending in the right direction. Uncertainty around the benefit in this subgroup is concerning, as patients in this subgroup are at greater risk with donanemab treatment due to a higher incidence of ARIA (including symptomatic and serious ARIA) compared with heterozygotes and non-carriers. Whilst it is acknowledged that homozygous subjects are one of the smaller subgroups tested, these findings raised significant concerns about the benefit in these subjects and the benefit/risk given their higher risk with treatment.

Reduction in amyloid plaque was observed regardless of E4 allele number although the reduction was smaller among those with two E4 alleles.

Regarding analysis of amyloid PET, in the intermediate and overall tau population, donanemab-treated participants had statistically significantly more amyloid plaque reduction compared with placebo-treated participants as assessed by the amyloid PET measurement (Centiloid units, CL) at Week 76.

A total of 34% in the intermediate tau population and 30% donanemab-treated participants in the overall population had amyloid clearance defined as an amyloid plaque level of less than 24.1 CL at as early as Week 24 ($p<.0001$).

At Week 76, statistically significant results in amyloid clearance were observed in donanemab-treated participants compared with placebo-treated participants in both intermediate tau and overall populations ($p<.0001$).

Therefore, donanemab's ability to significantly reduce amyloid's plaque is not questioned. However, data from both studies (AACG and AACI) showed that, at week 76, there was not a statistically significant correlation between change from baseline to endpoint in amyloid PET biomarker values and change from baseline to endpoint in clinical efficacy scales.

IV.5 Clinical safety

The safety profile of donanemab is predominately based on the integrated safety results of key registration Studies AACI-PC (AACI placebo-controlled period) and AACG in addition to the following studies:

- a safety addendum that is part of Study AACI (AACI Safety Addendum)
- an extension period that is part of Study AACI (AACI-long-term extension)
- an extension study for completers of Study AACG (Study AACH),
- an active comparator study of donanemab and aducanumab (Study AACN).

For the exposure evaluations, all participants were considered to have the following exposures based on the number of donanemab infusions received:

- 1 day of exposure = 1 infusion
- 3 months of exposure = 3 infusions
- 6 months of exposure = 6 infusions,
- 12 months of exposure = 12 infusions.

A total of 941 participants received at least 1 infusion of initial 700 mg. Participants receiving the recommended dosing regimen of 3 infusions of 700 mg followed by infusions of 1400 mg are summarised in Table 33 on the following page.

Table 33: Donanemab exposures at recommended dosing regimen.

	Placebo-Controlled Exposures	Donanemab-Treated Integrated Exposures
	Dona-PC, LY only (AACG[a], AACI) **N=984** Nx=941	**All Dona** (AACG[a], AACI[b], AACI Safety Addendum, AACH Part B, AACN Dona Cohort) **N=2727** Nx=2684
N who received 3 doses of 700 mg	882	2308
≥6 months (24 weeks), Infusion 6	696	1678
≥12 months (52 weeks), Infusion 12	473	964
72 weeks, Infusion 19	179	215
76 weeks, Infusion 19[c]	179	215
102 weeks, Infusion 26	0	8

Abbreviations: AACG = Study I5T-MC-AACG; AACH = Study I5T-MC-AACH; AACI = Study I5T-MC-AACI; AACN = Study I5T-MC-AACN; BACE = β-site amyloid precursor protein-cleaving enzyme; Dona = donanemab; LY = LY3002813; LTE = long-term extension; N = number of participants in the analysis populationNx = number of participants in the analysis population who received at least 1 initial dose of 700 mg; n = number of participants; PC = placebo controlled.

[a] Includes only participants from Study AACG who received donanemab as monotherapy (n=131). Does not include participants who received donanemab plus BACE inhibitor (n=15, combination arm).

[b] Study AACI main includes AACI-PC and AACI-LTE.

[c] Week 76 is the last visit of the double-blind treatment period and is 4 weeks after last infusion at Week 72. The next infusion for those proceeding to the LTE is Week 78.

From the All Dona exposure data, 2308 patients received 3 doses of 700mg of Donanemab. 215 patients received 19 infusions up to week 76 and 8 patients received 26 infusions up to week 102.

Adverse events

In the controlled studies, the percentage of deaths was slightly higher for the donanemab treated group (1.7%) compared to the placebo treated group (1.2%). SAEs were also higher for the donanemab group (17.1% vs 15.3%) and in particular for 'discontinuation from study due to an AE' (9.1% Donanemab vs 4.1% for PBO) and 'discontinuation from study treatment due to an AE' (15.4% Donanemab vs 4.7% for PBO).

Table 34: Common treatment-emergent adverse events occurring in ≥5% of placebo-controlled donanemab-treated participants, by preferred term within system organ class Dona-PC and All Dona.

Number of Participants	DONA-PC		ALL DONA
	Placebo (N=999) n (%)	Donanemab (N=984) n (%)	Donanemab N=2727 n (%)
Nervous system disorders	248 (24.8)	459 (46.6)	1218 (44.7)
Amyloid-related imaging abnormality-oedema/effusion	18 (1.8)	240 (24.4)	531 (19.5)
Amyloid-related imaging abnormality-microhaemorrhages and haemosiderin deposits	69 (6.9)	179 (18.2)	431 (15.8)
Superficial siderosis of central nervous system	14 (1.4)	76 (7.7)	149 (5.5)
Headache	101 (10.1)	129 (13.1)	294 (10.8)
Dizziness	63 (6.3)	64 (6.5)	143 (5.2)
Injury, poisoning and procedural complications	145 (14.5)	225 (22.9)	722 (26.5)
Fall	129 (12.9)	131 (13.3)	305 (11.2)
Infusion related reaction	4 (0.4)	84 (8.5)	225 (8.3)
Gastrointestinal disorders	75 (7.5)	103 (10.5)	419 (15.4)
Nausea	38 (3.8)	51 (5.2)	86 (3.2)
Musculoskeletal and connective tissue disorders	71 (7.1)	80 (8.1)	443 (16.2)
Arthralgia	52 (5.2)	59 (6.0)	102 (3.7)

Abbreviations: Dona = donanemab; N = number of participants; n = number of subjects with at least 1 TEAE; PC = placebo controlled; TEAE = treatment-emergent adverse event.
Sources: Table APP.2.7.4.7.A-14 and Table APP.2.7.4.7.A-15

In the donanemab treated and placebo-controlled group, the most frequently reported TEAEs for donanemab-treated participants were ARIA-related events of oedema/effusion (24.4% Donanemab vs 1.8% for PBO) and microhaemorrhage/haemosiderin deposits (18.2% donanemab vs 6.9% PBO), in the Nervous system disorders system organ class.

Therefore, common TEAEs of ARIA-E, ARIA-H, IRR, nausea, vomiting, and headache have been more commonly observed in the donanemab-treated population and have been identified as ADRs based on the review of data and biological plausibility.

The most frequently reported TEAEs in All Dona were ARIA-E, ARIA-H, and headache. Most of the common AEs in All Dona were similar to those observed in Dona-PC with the exception of nausea and arthralgia, which were present at less than 5% in All Dona.

In the DONA-PC group, most participants reported TEAEs that were of mild (placebo, 36.7%; donanemab, 34.9%) or moderate severity (placebo, 36.9%; donanemab, 41.9%). Severe TEAEs were reported in approximately 9.5% of placebo-treated participants compared with 12.5% of donanemab-treated participants.
Severe TEAEs that occurred at a frequency of at least 1% and were reported in more than 1 patient in the donanemab treatment group in Dona-PC included Amyloid-related imaging abnormality-oedema/effusion (placebo 0% and donanemab 2.1%).

In the All-Dona group, most participants reported TEAEs that were of mild (33.8%) or moderate severity (33.7%). Severe TEAEs that occurred at a frequency of at least 1% and were reported in more than 1 patient in All Dona included Amyloid-related imaging abnormality-oedema/effusion (1.5%).

Table 35: Serious adverse events occurring in >0.5% of donanemab-treated participants (Dona-PC) by preferred terms within System Organ Class whilst on treatment Dona-PC and All Dona.

Number of Participants	DONA-PC		ALL DONA
	Placebo (N=999) n (%)	Donanemab (N=984) n (%)	Donanemab (N=2727) n (%)
Subjects ≥1 SAE	153 (15.3)	168 (17.1)	411 (15.1)
Nervous system disorders	29 (2.9)	45 (4.6)	109 (4.0)
Amyloid-related imaging abnormality-oedema/effusion	0	15 (1.5)	26 (1.0)
Syncope	11 (1.1)	10 (1.0)	25 (0.9)
Infections and infestations	31 (3.1)	32 (3.3)	84 (3.1)
Pneumonia	6 (0.6)	10 (1.0)	17 (0.6)
COVID-19	4 (0.4)	8 (0.8)	18 (0.7)
Respiratory, thoracic and mediastinal disorders	9 (0.9)	12 (1.2)	28 (1.0)
Pulmonary embolism	2 (0.2)	6 (0.6)	10 (0.4)

Abbreviations: Dona = donanemab; COVID-19 = coronavirus disease 2019; N = number of participants; n = number of participants with events meeting specified criteria; PC = placebo controlled; SAE = serious adverse event.
Sources: Table APP.2.7.4.7.A-24 and Table APP.2.7.4.7.A-25

For Dona-PC, the overall percentage of participants who had 1 or more SAEs was similar in the placebo and donanemab groups. When SAEs were evaluated using All Dona, similar frequencies were noted to those from the Dona-PC

Serious adverse events and deaths
Through the data cutoff dates, deaths have been reported for participants in Dona-PC: placebo (n=12, 1.2%), and donanemab (n=17, 1.7%).

Fatal events reported as cause of death in 2 or more participants in either treatment group were:

- Placebo-treated group - Pneumonia (2 participants)
- Donanemab-treated group – Death (3 participants), Completed suicide (2 participants), COVID-19 (2 participants, 1 with pneumonia), and Pulmonary embolism (2 participants).

A total of 3 participants in the donanemab-treated group reported serious ARIA and subsequently died. One (0.1%) death was attributed to ARIA-E, 1 (0.1%) death to ARIA-H, and the third participant died after an incident of serious ARIA-E and ARIA-H.

In the All Dona group, an additional 15 deaths were reported in donanemab-treated participants for a total of 32 deaths (1.2%). One additional ‘death’ was reported for a donanemab-treated participant and 2 deaths were reported as dehydration; all other deaths were single event terms. Four deaths were reported in participants who did not meet criteria for inclusion in the predefined analysis sets (that is, the 57-day criteria). Four of the five deaths considered drug-related by the investigators, were in donanemab treated patients. Of the donanemab treated patients, 3 deaths were APOE4 carrier and one was a non-carrier.

Table 36 presents SAEs reported in more than 0.5% of participants in the donanemab treated group, compared with corresponding frequencies in All Dona. The overall percentage of participants who had 1 or more SAEs was similar in the placebo and donanemab groups. When SAEs were evaluated using All Dona, similar frequencies were noted to those from the Dona-PC AS.

Table 36: Serious adverse events occurring in >0.5% of Donanemab-Treated Participants (Dona-PC) by preferred terms within System Organ Class while on treatment.

Number of Participants	DONA-PC		ALL DONA
	Placebo (N=999) n (%)	Donanemab (N=984) n (%)	Donanemab (N=2727) n (%)
Subjects ≥1 SAE	153 (15.3)	168 (17.1)	411 (15.1)
Nervous system disorders	29 (2.9)	45 (4.6)	109 (4.0)
Amyloid-related imaging abnormality-oedema/effusion	0	15 (1.5)	26 (1.0)
Syncope	11 (1.1)	10 (1.0)	25 (0.9)
Infections and infestations	31 (3.1)	32 (3.3)	84 (3.1)
Pneumonia	6 (0.6)	10 (1.0)	17 (0.6)
COVID-19	4 (0.4)	8 (0.8)	18 (0.7)
Respiratory, thoracic and mediastinal disorders	9 (0.9)	12 (1.2)	28 (1.0)
Pulmonary embolism	2 (0.2)	6 (0.6)	10 (0.4)

Abbreviations: Dona = donanemab; COVID-19 = coronavirus disease 2019; N = number of participants; n = number of participants with events meeting specified criteria; PC = placebo controlled; SAE = serious adverse event.
Sources: Table APP.2.7.4.7.A-24 and Table APP.2.7.4.7.A-25

The percentage of participants who discontinued study treatment due to an AE was lower in the placebo treatment group (4.7%) compared with the donanemab treatment group (15.4%). Events reported in at least 1% (after rounding) of participants in Dona-PC that led to permanent discontinuation of study treatment were provided. The events were in the Nervous system disorders and Injury, poisoning and procedural complications system organ classes.

9.7% of participants in the All Dona AS discontinued study treatment due to an AE.
The most frequently reported events that led to permanent discontinuation of donanemab were in the Nervous system disorders and Injury, poisoning and procedural complications system organ classes. The most commonly reported events (1.0% after rounding or more of participants) remained IRR, ARIA-E, ARIA-H, and SS of central nervous system.

The adverse events were analysed by system organ class. The 3 most common system organ classes in both the Dona-PC groups and All Dona group were nervous system disorders, infections and infestations, and injury, poisoning and procedural complications.

Treatment emergent adverse events were also evaluated in Dona-PC using MedDRA PT nested within FMQ (FDA Medical Queries) narrow PTs. The FMQs with higher frequency of events in the donanemab group included:

- Headache (placebo n=105, 10.5%; donanemab n=139, 14.1%)
- Local administration reaction (placebo n=26, 2.6%; donanemab n=108, 11.0%)
- Lipid disorder (placebo n=6, 0.6%; donanemab n=19, 1.9%)
- Hypersensitivity (placebo n=3, 0.3%; donanemab (n=16, 1.6%)
- Erythema (placebo n=2, 0.2%; donanemab n=12, 1.2%).

In summary, the most frequently reported TEAEs for donanemab-treated participants were ARIA-related events of oedema/effusion (24.4% Donanemab vs 1.8% for PBO) and microhaemorrhage/haemosiderin deposits (18.2% donanemab vs 6.9% PBO), in the Nervous system disorders SOC. Therefore, Common TEAEs of ARIA-E, ARIA-H, IRR, nausea, vomiting, and headache have been more commonly observed in the donanemab-treated population and have been identified as ADRs based on the review of data and biological plausibility**.**

Severe TEAEs were reported in approximately 9.5% of placebo-treated participants compared with 12.5% of donanemab-treated participants. Amyloid-related imaging abnormality-oedema/effusion occurred at a frequency of at least 1% and were reported in more than 1 patient in the donanemab treatment group in Dona-PC included (placebo 0% vs donanemab 2.1%).

Four of the five deaths considered drug-related by the Investigators, were in donanemab treated patients where cause of death were brain haemorrhages showing after the third dose. . Of the donanemab treated patients, 3 deaths were APOE ε3ε4 carriers, and 1 was a non-carrier.

Laboratory findings

Mean laboratory values and changes from baseline to any time postbaseline for donanemab treated participants were generally minimal and similar to those seen in placebo-treated participants.

Increases in mean CPK were observed in the donanemab group compared with the placebo group at W24 and W36 due to 4 participants. However, no consistent increase was observed, and the overall distribution of values was similar between the placebo and the donanemab groups as indicated by similar quartile and median values at all visits. Four participants had a Grade 4 increase of CPK. None appeared to be associated with donanemab treatment.

In all Dona analysis sets, Laboratory analyte decreases were for haematology were seen in:

- 5 (0.2%) participants with a CTCAE Grade 3 decrease in leukocytes
- 25 (1.1%) with a CTCAE Grade 3 decrease in lymphocytes, and
- 9 (0.4%) with a CTCAE Grade 3 decrease in neutrophil count, including 1 patient with a neutrophil decrease of CTCAE Grade 4.

The magnitude of changes in the other laboratory parameters assessed using mean values and changes from baseline was small, and no trends were observed. Any observed differences between treatment groups were evaluated and were found to be neither consistent nor clinically meaningful.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Dona-PC Mean changes from baseline to any time postbaseline in vital sign parameters, including orthostatic changes, as well as body weight and temperature changes, were similar in donanemab- and placebo-treated participants. The magnitude of change in vital sign parameters was small and the observed differences between treatment groups were not considered clinically meaningful.

Changes in ECG parameters were assessed. Results of analyses for TE vital signs did not show any particular pattern of abnormalities associated with donanemab treatment.

Analyses for Dona-PC detected no clinically meaningful findings in the vital sign measurements. Mean changes from baseline to any time postbaseline in ECG parameters were generally minimal for donanemab-treated participants and were assessed as not clinically meaningful.

Safety in special groups and situations

Dona-PC and All Dona were used to provide an overview of AEs by age category. In addition, Dona-PC was used for all analyses done to determine the overall incidence of common TEAEs by intrinsic factors including age, sex, race, ethnicity, and APOE ε4 carrier status.

No clinically meaningful interactions of ethnicity, race, sex or age on the frequency of common TEAEs were noted. No clinically meaningful interactions of geographic region and treatment group on the frequency of common TEAEs were noted.

Amyloid-Related Imaging Abnormalities

Amyloid-Related Imaging Abnormalities were evaluated in donanemab treated patients. An increased risk of both ARIA-E and ARIA-H with anti-amyloid antibody is recognised. Risk factors reported in the literature as being associated with ARIA-H include APOE ε4 alleles, preexisting ARIA-H microhaemorrhages, and the use of antithrombotics.

Table 37: ARIA-H and macrohaemorrhage frequency by MRI.

	DONA-PC N=1983		ALL DONA N=2727
	Placebo n=999	Donanemab n=984	Donanemab N=2727
ARIA-E and/or ARIA-H	136 (13.6)	360 (36.6)	819 (30.0)
Concurrent ARIA-E and ARIA-H[a]	6 (0.6)	161 (16.4)	345 (12.7)
Serious ARIA (-E or -H)	0	10 (1.0)	22 (0.8)
ARIA-H	124 (12.4)	307 (31.2)	697 (25.6)
Isolated ARIA-H	117 (11.7)	123 (12.5)	292 (10.7)
ARIA-H microhaemorrhage	109 (10.9)	246 (25.0)	576 (21.1)
Isolated ARIA-H microhaemorrhage	93 (9.3)	79 (8.0)	205 (7.5)
ARIA-H superficial siderosis	28 (2.8)	157 (16.0)	327 (12.0)
Isolated ARIA-H superficial	15 (1.5)	26 (2.6)	50 (1.8)
Macrohaemorrhage[b]	2 (0.2)	3 (0.3)	7 (0.3)
Isolated macrohaemorrhage	0	1 (0.1)	1 (0.0)
Serious macrohaemorrhage	0	1 (0.1)	2 (0.1)

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA-oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition; Dona = donanemab; MRI = magnetic resonance imaging; N = number of subjects in the analysis population; n = number of subjects within each specific category; PC = placebo controlled.

a Concurrence is defined as ARIA-E and ARIA-H occurring on the same MRI.

b Macrohaemorrhage is defined as >10 mm in diameter.

Sources: Table 2.7.4.25 and Table 2.7.4.26

In study AACI the incidence of ARIA-E based on MRI or TEAE cluster was higher in the donanemab group (24.0%) compared to the placebo group (2.1%). Symptomatic ARIA -E occurred in 5.8%. The most reported symptoms (>0.5% participants treated with donanemab) associated with ARIA-E were headache, confusional state, dizziness, nausea and seizure. Most ARIA-E cases were mild or moderate in severity. A total of 13 (1.5%) donanemab-treated patients had serious ARIA cases.

In the donanemab studies, most ARIA-E events were first observed within 12 weeks of treatment, and most ARIA-H events were first observed within 24 weeks of treatment. Median time to resolution was approximately 9 weeks (59 days) for ARIA-E in donanemab-treated participants.

The incidence of ARIA-H (donanemab group: 31.4%; placebo group: 13.6%) based on MRI or TEAE cluster was higher in the donanemab-treated participants compared with the placebo -treated participants. Serious ARIA-H occurred in 4 (0.5%) of donanemab-treated participants.

Three participants with serious ARIA subsequently died; the cause of death was related to ARIA-E for 1 participant, ARIA-H for another participant, and the third participant had serious ARIA-E and ARIA-H prior to death.

APOE Ɛ4 genotype was associated with ARIA risk. For overall ARIA-E and ARIA-H, the APOE Ɛ4 homozygous has the highest risk, followed by APOE Ɛ4 heterozygous, and the noncarriers have the lowest risk while controlling for other potential risk factor.

The frequency of ARIA-H (based on MRI and TEAE cluster) was the highest in donanemab -treated homozygote APOE ε4 carriers:

- homozygote APOE ε4 carriers (43.2%)
- heterozygote APOE ε4 carriers (26.2%), and
- noncarriers (16.6%).

Similar findings were observed for ARIA-H Microhaemorrhage and ARIA-H SS.

Additional analyses include evaluation of severe ARIA-H by APOE ε4 status. The frequency of severe ARIA-H events by APOE ε4 status is as follows:

- donanemab-treated homozygote APOE ε4 carriers: 19.3%
- donanemab-treated heterozygote APOE ε4 carriers: 7.2%, and
- noncarriers: 3.5%.

In line with what has been reported with other monoclonal antibody therapies directed against aggregated forms of beta amyloid, APOE4 homozygotes treated with donanemab have a higher incidence of ARIA (E and H), including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers.

The cases of macrohaemorrhage were limited and were not associated with APOE Ɛ4 status. The benefit risk balance in APOE4 homozygous patients is of particular concern given their increased risk of ARIA compared to heterozygotes and non-carriers.

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.

ARIA-E and ARIA-H severity by MRI was mostly mild to moderate.

When comparing within treatment for both donanemab- and placebo-treated participants, the observed frequency of ARIA in participants using antithrombotic medications (at any time or within 30 days prior to the event) and those not using antithrombotic medications was similar.

The findings were similar for concomitant use/non-use of aspirin, non-aspirin anti -platelets, or anticoagulants within both treatment groups. However, since analysis for participants with concomitant use of thrombolytics is limited by the low numbers of participants using these medications a conclusion on the risk of ARIA associated with concomitant use of these drugs cannot be established.

Donanemab-treated participants who had ARIA-H had similar frequency of using antithrombotic medications (at any time or within 30 days prior to the event) than not using antithrombotic medications before an ARIA-H event. Section 4.4 of the SmPC describes these findings and the uncertainties of this correlation due to limited data and caution when considering the administration of anti-thrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with donanemab, is recommended.

Consistent across all analyses are the association of APOE Ɛ4, superficial siderosis and microhaemorrhage at baseline with an increased risk of ARIA-E, symptomatic ARIA-E, and ARIA-H.

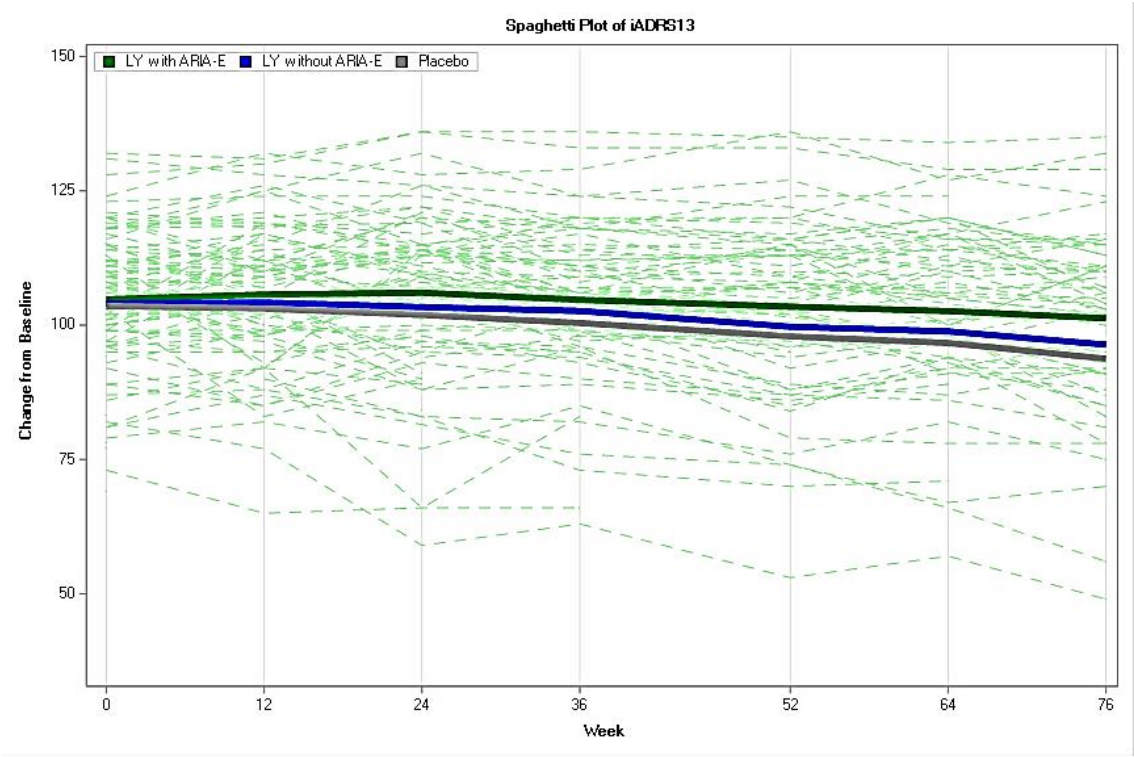
Regarding ARIA-H recurrence, most of the All-Dona participants with ARIA-H experienced at least 1 episode of ARIA-H (n=697, 25.6%), followed by those experiencing at least 2 episodes of ARIA-H (n=237, 8.7%). A maximum of 6 episodes was experienced by 1 participant.

The applicant investigated any impact of ARIA events on cognitive function, both in subjects that had single events and those that had recurrent events. To evaluate the clinical status of individual study participants before and after ARIA, The applicant presented spaghetti plots showing iADRS scores over 76 weeks for those who had an observation of ARIA-E

- by 12 weeks,
- between 12 and 24 weeks,
- after 24 weeks, or
- that was recurrent (more than one episode of ARIA-E).

It is difficult to interpret individual clinical trajectories for those on donanemab with ARIA- without individual clinical trajectories for those on donanemab without ARIA-E. However, the average lines for each group (donanemab with ARIA-E, donanemab without ARIA-E, placebo) do not suggest that those on donanemab with ARIA-E experienced greater decline on the iADRS score than those on donanemab without ARIA-E or those on placebo.

Figure 54: Spaghetti plot: iADRS for LY-treated participants experiencing ARIA-E ≤ 12 weeks in Study AACI-PC.



Abbreviations: ARIA-E = amyloid-related imaging abnormalities – edema; iADRS = integrated Alzheimer's Disease Rating Scale; LY = LY3002813 (donanemab).

Figure 55: Spaghetti plot: iADRS for LY-treated participants experiencing ARIA-E >12 Weeks and ≤24 weeks in Study AACI-PC.

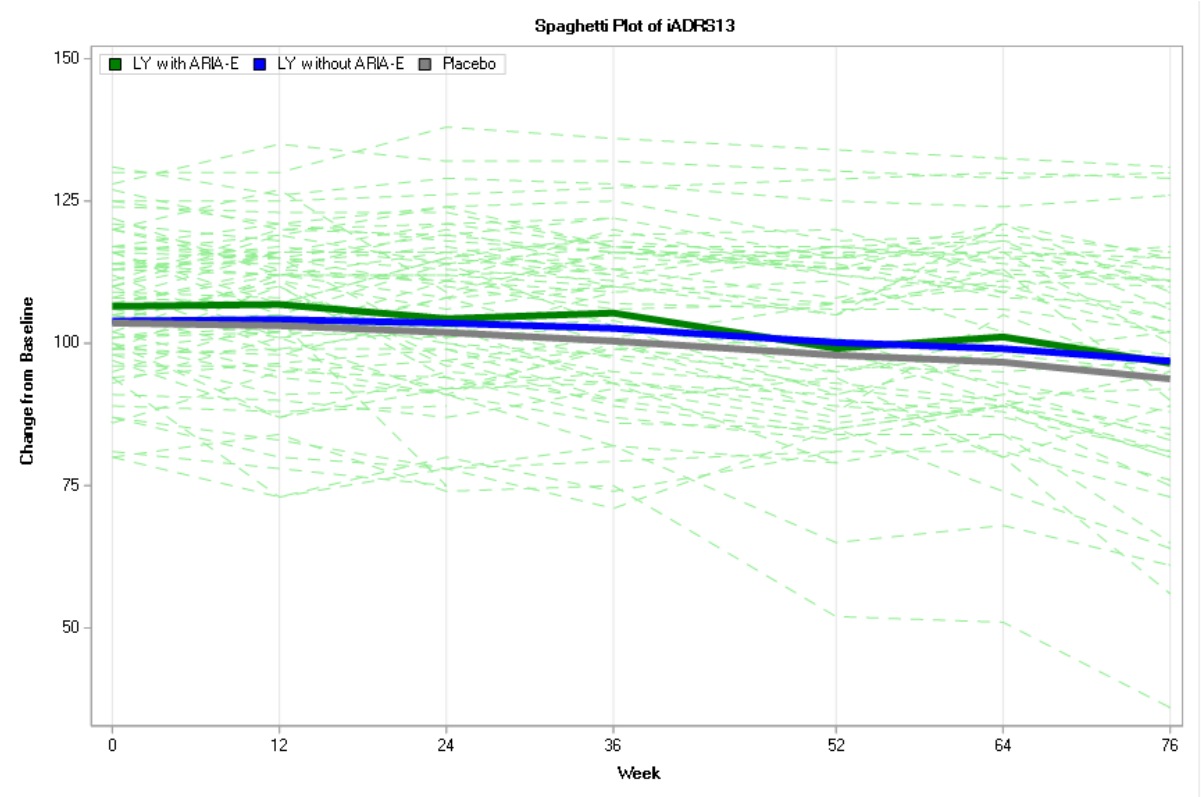


Figure 56: Spaghetti plot: iADRS for LY-treated participants experiencing ARIA-E >24 weeks in Study AACI-PC.

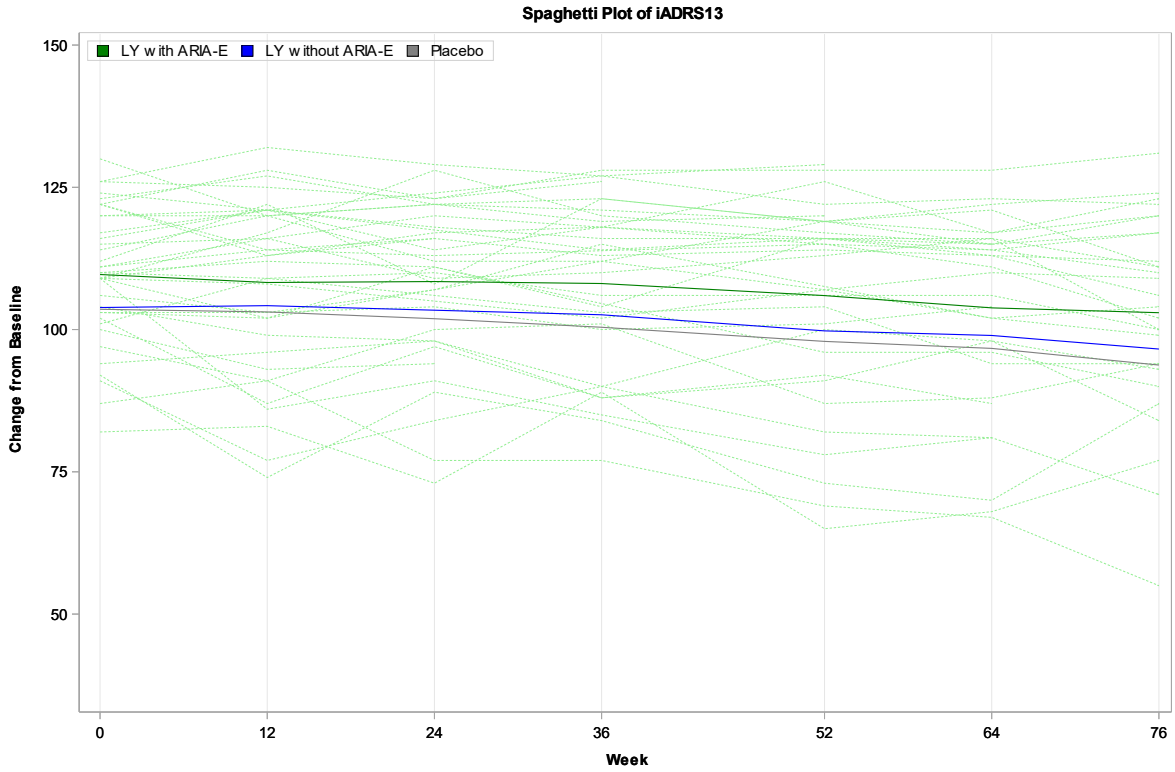
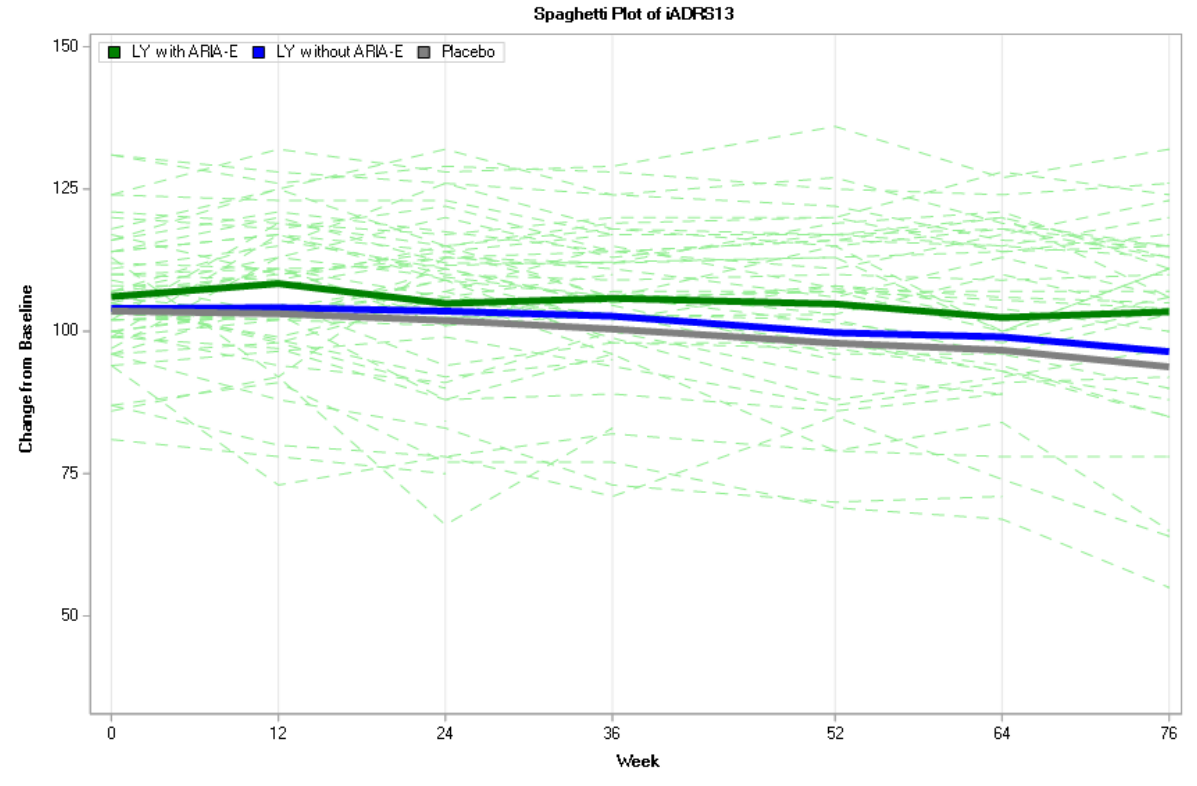


Figure 57: Spaghetti plot: iADRS for LY-treated participants experiencing recurrent ARIA-E events in Study AACI-PC.



As presented, the data suggest that, on average, those on donanemab with ARIA-E may have experienced less progression than those on donanemab without ARIA-E. However, with the exception of those who experienced ARIA-E before 12 weeks (who had similar baseline iADRS score to other groups), those on donanemab with ARIA-E had a better overall iADRS score than other groups to begin with.

In summary, the increased risk of both ARIA-E and ARIA-H with anti-amyloid antibody is recognised and has also been confirmed from the donanemab studies.

Hepatic safety

No adverse hepatic effects were observed in nonclinical studies. In clinical pharmacology studies, no clinically meaningful alterations in hepatic laboratory values were observed. Overall, no differences between donanemab- and placebo-treated participants were observed in the results based on analysis of laboratory parameters, and TEAEs related to hepatic function and injury were reported.

Categorical shift analyses revealed no differences in hepatic laboratory parameters related to hepatic function and injury in the Dona-PC or All Dona groups.

Suicidal Ideation and Behaviour

Studies included assessment of any occurrence of suicide-related thoughts and behaviours as assessed using the C-SSRS. The C-SSRS standard version was used in the Phase 2 and 3 studies, while the C-SSRS Children's version was used in Phase 1 Studies AACC and AACD.

Preexisting depression was generally balanced across the placebo and donanemab treatment groups of the Dona-PC analysis set, with 24.9% of participants in the placebo arm and 23.9% of participants in the donanemab arm. Overall, 4 SAEs of suicidal ideation and behaviour were reported in the donanemab group and 2 SAEs in the placebo group. Of these SAEs, 3 were fatal; 2 in the donanemab group and 1 in the placebo group.

Based on available data, donanemab is not expected to be associated with an increased risk of suicidal ideation or behaviour.

Immunological events

Due to early observation of infusion related reactions (IRRs) in Phase 1 clinical studies, suspected hypersensitivity, anaphylaxis, and IRR events were carefully monitored in subsequent studies and deemed AESIs to better characterise these events.

Hypersensitivity reactions are a known safety signal with the use of monoclonal antibodies directed against aggregated forms of beta amyloid.

A higher frequency of immediate hypersensitivity events was reported for donanemab-treated participants (10.2%) compared with those treated with placebo (1.0%).

The severity of the following TEAES are shown below:

- IRR TEAEs was mild (56.5%), moderate (38.4%), and severe (5.1%)
- anaphylactic reaction TEAEs was mild (37.5%), moderate (50%), and severe (12.5%), and
- hypersensitivity TEAEs was mild (33.3%), moderate (46.7%), and severe (20%).

Immediate Symptoms Reported from Immediate Hypersensitivity, Anaphylaxis, and Infusion-Related Reactions occurring in more than 1% of donanemab-treated participants included in decreasing order: nausea or vomiting, chills, erythema, headache, low blood pressure, difficulty breathing or dyspnoea, elevated blood pressure, and sweating. Chest pain, tight chest, or chest discomfort collectively were also frequently reported.

Among 984 donanemab-treated participants, 82 (8.3%) reported a PT of Infusion related reaction on the day of infusion: (32.9%) in the upper ADA titre group, (7.1%) in the middle ADA titre group and (2.3%) in the lower ADA titre group.

Recommendations for monitoring and management of infusion related reactions are included in the product information.

Other safety aspects

No pharmacokinetic drug interactions are expected based on the characteristics of donanemab and no drug interaction studies were conducted. However, ARIA-H including events of cerebral haemorrhage are a recognised adverse reaction with donanemab treatment. The potential for an increased risk of these events with concomitant antithrombotic medication has been previously discussed.

The incidence of TEAEs leading to discontinuation of study drug was higher in subjects receiving donanemab compared to placebo. The most frequent events resulting in donanemab discontinuation and at greater frequency than placebo were infusion related reactions, amyloid-related imaging abnormality-oedema/effusion, superficial siderosis of CNS and amyloid-related imaging abnormality-microhaemorrhage and hemosiderin deposits.
At the time of the application, there was no post-marketing experience available for donanemab as it was not marketed in any territory.

Conclusions on safety

The main safety signals that have been previously identified in association with the use of monoclonal antibodies directed against aggregated forms of beta amyloid are ARIA, cerebral haemorrhage, infusion related reactions and hypersensitivity.

The safety profile of donanemab is predominately based on the integrated safety results of key registration Studies AACI-PC (AACI placebo-controlled period) and AACG in addition to the following ongoing studies: AACI Safety Addendum, AACI-long-term extension, an extension study for completers of Study AACG (Study AACH), and an active comparator study of donanemab and aducanumab (Study AACN).

A total of 941 participants received at least 1 infusion of initial 700 mg. From the integrated exposure data, 2308 patients received 3 doses of 700mg of Donanemab. 215 patients received 19 infusions up to week 76 and 8 patients received 26 infusions up to week 102.

The most frequently reported TEAEs for donanemab-treated participants were ARIA-related events of oedema/effusion (24.4% Donanemab vs 1.8% for PBO) and microhaemorrhage/haemosiderin deposits (18.2% donanemab vs 6.9% PBO), in the Nervous system disorders system organ class.

Also, IRR, nausea, vomiting, and headache were more commonly observed in the donanemab-treated population and, therefore, have been identified as ADRs based on the review of data and biological plausibility.

Severe TEAEs were reported in approximately 9.5% of placebo-treated participants compared with 12.5% of donanemab-treated participants. Amyloid-related imaging abnormality-oedema/effusion occurred at a frequency of at least 1% and were reported in more than 1 patient in the donanemab treatment group in Dona-PC included (placebo 0% vs donanemab 2.1%).

In the controlled studies, the percentage of deaths was slightly higher for the donanemab treated group (1.7%) compared to the placebo treated group (1.2%).

Four of the five deaths considered drug-related by the Investigators, were in donanemab treated patients where cause of death were brain haemorrhages showing after the third dose. Of the donanemab treated patients, 3 deaths were APOE ε3ε4 carriers, and 1 was a non-carrier.

An increased risk of both ARIA-E and ARIA-H with anti-amyloid antibody is recognised. In the donanemab studies, most ARIA-E events were first observed within 12 weeks of treatment, and most ARIA-H events were first observed within 24 weeks of treatment.

Symptomatic ARIA-E occurred in 5.8% and SAEs associated with ARIA-E/H were reported in 1.6% of participants. Median time to resolution was approximately 9 weeks (59 days) for ARIA-E in donanemab-treated participants. Three participants with serious ARIA subsequently died; the cause of death was related to ARIA-E for 1 participant, ARIA-H for another participant, and the third participant had serious ARIA-E and ARIA-H prior to death. APOE Ɛ4 homozygous patients had the highest risk of developing ARIA, followed by APOE Ɛ4 heterozygous and the noncarriers. The frequency of ARIA-H was the highest in donanemab-treated homozygote APOE ε4 carriers (homozygote APOE ε4 carriers (43.2%); heterozygote APOE ε4 carriers (26.2%), and noncarriers (16.6%).

Consistent across all analyses are the association of APOE Ɛ4, superficial siderosis and microhaemorrhage at baseline with an increased risk of ARIA-E, symptomatic ARIA-E, and ARIA-H.

These findings are in-line with what has been reported with other monoclonal antibody therapies directed against aggregated forms of beta amyloid.

The cases of macrohaemorrhage were limited and were not associated with APOE Ɛ4 status. Based on these results, the benefit risk balance in APOE4 homozygous patients is of particular concern. As such, donanemab is indicated in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers for the treatment of mild cognitive impairment and mild dementia due to Alzheimer’s disease.

In contrast with what has been reported with other monoclonal antibody therapies directed against aggregated forms of beta amyloid, the frequency of ARIA-H in participants using antithrombotic medications (at any time or within 30 days prior to the event) and those not using antithrombotic medications was similar between active treatment and placebo groups.

The findings were similar for concomitant use/non-use of aspirin, non-aspirin anti-platelets, or anticoagulants within both treatment groups.

However, since analysis for participants with concomitant use of thrombolytics is limited by the low numbers of participants using these medications a conclusion on the risk of ARIA associated with concomitant use of these drugs cannot be established. These findings and the uncertainties of this correlation due to limited data are reflected in the product information with a recommendation to use caution when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with donanemab.

Most of the All-Dona participants with ARIA-H experienced at least 1 episode of ARIA-H (n=697, 25.6%), followed by those experiencing at least 2 episodes of ARIA-H (n=237, 8.7%). A maximum of 6 episodes was experienced by 1 participant.

A higher frequency of immediate hypersensitivity events was reported for donanemab-treated participants (10.2%) compared with those treated with placebo (1.0%). The adverse events are reflected in the product information.

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. In addition to routine measures, the additional pharmacovigilance and risk minimisation measures in the following table have been proposed.

Table 38: Summary of risk minimisation measures and additional pharmacovigilance activities.

Important Identified Risk: ARIA-E (cerebral oedema/effusion)	
Evidence for linking the risk to the medicine	ARIA-E is a known class effect of amyloid-targeting therapies. Patients with ARIA-E are usually asymptomatic. If symptoms occur, these may include, but are not limited to: • headache • vomiting • unsteadiness • dizziness • tremor • confusion • visual disturbances • speech disturbances • worsening cognitive function • alteration of consciousness, and • seizures. Intervention beyond withholding treatment may be required to address concomitant symptoms (for example, corticosteroids). ARIA-E was determined to be an important identified risk following a thorough review of the donanemab clinical programme data.
Risk factors and risk groups	In the donanemab clinical development program, a higher frequency of ARIA-E was observed in participants with baseline risk factors that

	included: • increased dose of donanemab • apolipoprotein E ε4 (APOE ε4) gene status; ARIA E frequency was increased in patients with one (heterozygotes) or two copies (homozygous) compared to those with no copies (non-carriers) of the ApoE ε4 gene, with those homozygous for APOE ε4 at greatest risk, and • baseline MRI microhaemorrhages and/or superficial siderosis prior to treatment initiation indicative of presence of amyloid deposits in blood vessels.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8, and Section 2 and 4 of the PIL. • Recommendations for monitoring and management of ARIA-E, including symptomatic cases, are included in SmPC Sections 4.2 and 4.4, and Section 2 of the PIL. • Recommendations for monitoring and management of ARIA-E, including symptomatic cases, are included in SmPC Sections 4.2 and 4.4, and Section 2 of the PIL. • Dosing recommendations for donanemab treatment after ARIA-E is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in case of imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage are included in SmPC Section 4.3. • Contraindication for ongoing anticoagulant use included in SmPC Section 4.3. • Contraindications for use of donanemab in patient with APOE4 homozygotes included in SmPC 4.4 Other routine risk minimisation measures beyond the Product Information: None **Additional risk minimisation measures:** • HCP educational material • Patient Card • Controlled Access Programme (CAP)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Mandatory PASS: Registry-based observational study to characterise safety of donanemab in UK patients • Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Identified Risk: ARIA-H (cerebral microhaemorrhage and superficial siderosis)	
Evidence for linking the risk to the medicine	ARIA-H is a known class effect of amyloid-targeting therapies. Patients with ARIA-H are usually asymptomatic. ARIA-H may be related to vascular amyloid clearance with weakening and rupture of small blood vessels. Whereas ARIA-E is usually radiographically visible over the course of weeks or months. ARIA-H can remain permanently visible on subsequent imaging. If symptoms occur, they may include,

	• headache • worsening confusion • dizziness • visual disturbances • nausea, and • seizures ARIA-H was determined to be an important identified risk following a thorough review of the donanemab clinical programme data.
Risk factors and risk groups	In the clinical development programme of donanemab, a higher frequency of ARIA-H was observed in participants with baseline risk factors that included: • increased dose of donanemab • APOE ε4 gene status: ARIA-H frequency was increased in patients with one (heterozygotes) or two copies (homozygous) compared to those with no copies (non-carriers) of the ApoE ε4 gene, with those homozygous for APOE ε4 at greatest risk. • baseline MRI microhaemorrhages and/or superficial siderosis prior to treatment initiation indicative of presence of amyloid deposits in blood vessels. • use of antithrombotic medication
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4,1,4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 and 4 of the PIL. • Recommendations for monitoring and management of ARIA-H, including symptomatic cases, are included in SmPC Sections 4.2 and 4.4, and Section 2 of the PIL. • Dosing recommendations of donanemab treatment after ARIA-H is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in case of imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage are included in SmPC Section 4.3. • Cautionary language on concomitant use of donanemab with antithrombotic medication including thrombolytics is included in SmPC Sections 4.4 and 4.5. • Contraindication for ongoing anticoagulant use included in SmPC Section 4.3 • Contraindications for use of donanemab in patient with APOE4 homozygotes included in SmPC 4.4 Other routine risk minimisation measures beyond the Product Information: None **Additional risk minimisation measures:** • HCP educational material • Patient Card • Controlled Access Programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Mandatory PASS: Registry-based observational study to characterise safety of donanemab in UK patients • Secondary database study to characterise safety, drug utilisation, and

	effectiveness of additional risk minimisation activities in donanemab-treated patients See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Identified Risk: Hypersensitivity events (including IRR)	
Evidence for linking the risk to the medicine	Biological drugs represent foreign protein and thereby can elicit immediate and non-immediate hypersensitivity events, including infusion-related reaction (IRRs) and anaphylaxis. Immediate hypersensitivity reactions, including IRRs, are associated with donanemab treatment and were determined to be an important identified risk following a thorough review of clinical programme data.
Risk factors and risk groups	No specific risk factors have been identified for hypersensitivity reactions. In clinical studies, 88.1% of donanemab-treated patients developed antidrug antibodies (ADA) and all the patients with ADA had neutralising antibodies. All patients reporting IRRs had ADA, and higher ADA concentration was associated with increased incidence of IRRs/immediate hypersensitivity events.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.8, 6.1 and Sections 2 and 4 of the PIL • Contraindication for use in patients with prior history of serious hypersensitivity to donanemab is included in SmPC Section 4.3. • Recommendations for management of serious infusion-related reactions are included in SmPC Section 4.4, and Sections 2 and 4 of the PIL. • Immediate discontinuation of donanemab in case of serious infusion-related reactions or as clinically indicated is included in SmPC Section 4.4. • Contraindications for serious hypersensitivity to the active substance or to any of the excipients is included in SmPC section 4.3 and 6.1. Other routine risk minimisation measures beyond the Product Information: None **Additional risk minimisation measures:** • Controlled Access Programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Mandatory PASS: Registry-based observational study to characterise safety of donanemab in UK patients • Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk intracerebral haemorrhage >1 cm	
Evidence for linking the risk to the medicine	Serious (including fatal) cases of intracerebral haemorrhage > 1 cm have been observed with other amyloid-targeting therapies. To date, there has been no clear evidence of an increased risk of intracerebral haemorrhage > 1 cm in patients exposed to donanemab following a thorough review of the clinical programme data. Therefore, intracerebral haemorrhage > 1 cm is considered an important potential risk for donanemab and will be

	further characterised in ongoing clinical trials and planned post-marketing observational studies.
Risk factors and risk groups	Risk factors specifically associated with intracerebral haemorrhage in patients with AD included: • APOE ε4 gene status: increased risk of intracerebral haemorrhage in patients with one (heterozygotes) or two copies (homozygous) of the ApoE ε4 gene. • Baseline MRI microhaemorrhages and/or superficial siderosis prior to treatment initiation indicative of presence of amyloid deposits in blood vessels. All the above-mentioned risk factors might further increase the risk for haemorrhagic complications during thrombolytic or antithrombotic therapies. Overall, concomitant antithrombotic use did not impact the frequency, severity, or seriousness of intracerebral haemorrhagic events. More than 40% of participants in both treatment groups used concomitant antithrombotics. Among those receiving any antithrombotic medication, aspirin was the most frequent concomitant antithrombotic (approximately 80%), followed by anticoagulants (greater than 20%). Analysis of antithrombotic medication type (aspirin, non-aspirin antiplatelets, and anticoagulants) did not reveal any patterns different than that observed for antithrombotics overall. However, the number of events and the limited number of exposures to other non-acetylsalicylic acid including anticoagulants and thrombolytic medicines, limit a definitive conclusion about the risk of intracerebral haemorrhage in patients taking these antithrombotic medicines.
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 of the PIL. • Contraindications for use in case of imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage are included in SmPC Section 4.3, and Section 2 of the PIL. • Contraindication for ongoing anticoagulant use included in SmPC Section 4.3. • Contraindication on previous history of intracerebral haemorrhage is included in Section 2 of the PIL. • Cautionary language on concomitant use of donanemab with anti-thrombotic and anti-coagulant medication including thrombolytics is included in SmPC Section 4.5. • Dosing recommendations of donanemab on identification of intracerebral haemorrhage >1 cm is included in SmPC Section 4.2. Other routine risk minimisation measures beyond the Product Information: None **Additional risk minimisation measures:** • HCP educational material • Patient Card • Controlled Access Programme

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Mandatory PASS: Registry-based observational study to characterise safety of donanemab in UK patients • Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Accelerated Brain Volume Loss	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 5.1 • Description of accelerated brain volume loss included in SmPC section 5.1. Other routine risk minimisation measures beyond the Product Information: None **Additional risk minimisation measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Clinical study: • AACI-LTE study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Long-Term Safety	
Risk minimisation measures	**Routine risk minimisation measures:** Other routine risk minimisation measures beyond the Product Information: • None Additional risk minimisation measures: • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational study: • Mandatory PASS: Registry-based observational study to characterise safety of donanemab in UK patients Clinical study: • AACI-LTE study See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: AACI-PC = AACI-Placebo-Controlled Analysis Set; ADA = antidrug antibody; AD = Alzheimer's disease; All-Dona = Donanemab-Treated Integrated Analysis Set; APOE ε4 = apolipoprotein subtype E allele 4; ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA–oedema/effusions; ARIA-H = ARIA–haemorrhage/haemosiderin deposition; CAA = cerebral amyloid angiopathy; Dona-PC = Placebo-Controlled Analysis Set; HCP = healthcare professional; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PASS = post-authorisation safety study; PIL = patient information leaflet; SmPC = summary of product characteristics.

This is acceptable.

IV.7 Discussion on the clinical aspects

Donanemab has a clear impact on amyloid beta plaque, reducing this in a dose and time-dependant manner and has demonstrated statistically significant difference compared to placebo in the primary endpoint in both the phase 2 (AACG) and Phase 3 (AACI) clinical studies.

The adverse reactions of most concern with donanemab treatment are ARIA-E, ARIA-H and intracerebral haemorrhage >1cm. The risk of these events, and therefore of treatment with donanemab, is higher in certain patient populations in which the risks are subsequently considered to outweigh the benefits.

These groups are:

- APOE4 homozygous patients: due to the increased incidence of ARIA, including symptomatic and serious ARIA compared with heterozygotes and non-carriers.
- Patients on anticoagulants: due to the increased risk of intracerebral macrohaemorrhage with donanemab treatment.
- Patients with cerebral amyloid angiopathy: the risk of ARIA and intracerebral haemorrhage is increased in these patients (patients with findings suggestive of severe CAA on MRI were excluded from the core clinical trials).

Donanemab use should be limited to patients with MCI due to AD and mild AD where the benefit-risk is clearest, and the benefits are considered to outweigh the risks.

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 (AD) in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers.

Kisunla 350 mg Concentrate for solution for infusion has been authorised with the condition to perform further studies and to provide additional measures to minimise the risk. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
1. IMPOSED UK DONANEMAB CONTROLLED ACCESS PROGRAMME A) In order to promote the safe and effective use of donanemab, initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme. 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 donanemab, 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 donanemab 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 and patients or carers. 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. 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	**To be implemented before product launch. Progress report submission dates aligned to periodic safety update report cycle**
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 MAH should ensure that all healthcare professionals who are expected to prescribe or monitor donanemab have access to/are provided with the following educational programme: • the summary of product characteristics • healthcare professional guide • a patient card.	**To be implemented before product launch**
3. IMPOSED POST AUTHORISATION SAFETY STUDY (CATEGORY 1) To investigate the safety and benefit-risk profile of donanemab 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.	**Draft protocol to be submitted within 6 Months of GB Regulatory Approval** **Study progress reports to be provided with The PSUR/PBRER** **Final study report submission date**

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	**to be determined**

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 SmPC and PIL 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**