14 November 2024
EMA/CHMP/573107/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Leqembi

International non-proprietary name: lecanemab

Procedure No. EMEA/H/C/005966/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

µg	microgram
Aβ	Beta-Amyloid
AD	Alzheimer's Disease
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody Dependent Cellular Phagocytosis
ADME	Absorption, Distribution, Metabolism and Excretion
AEX	Anion Exchange (Chromatography)
AUC	Area Under the Concentration-time curve
Aβ	Amyloid beta
BLQ	Below Limit of Quantification
C1q	Complement Component 1q
CAPA	Corrective Action/Preventive Action
CCS	Container Closure System
CFU	Colony Forming Unit
CHMP	Committee For Evaluation Of Human Medicinal Products
CHO	Chinese Hamster Ovary
Cmax	maximum plasma concentration
CNS	Central Nervous System
CQA	Critical Quality Attribute
CSF	Cerebro spinal fluid
CT	computed tomography
CV	coefficient of variation
DNA	Deoxyribose Nucleic Acid
EC	European Commission
EMA	European Medicines Agency
FcγRI	Fc Gamma Receptor I (CD64)
FcγRIIa	Fc Gamma Receptor Iia (CD32a)
FcγRIIIa	Fc Gamma Receptor Iiia (CD16a)
FcRn	Neonatal Fc Receptor
FcγR	Fc gamma receptor
GMP	Good Manufacturing Practice

h	hour
HC	Heavy Chain
i.e.	id est
IC50	Concentration that resulted in 50% inhibition
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
Ig	immunoglobulin
IgG	Immunoglobulin G
KD	dissociation constant
LC	Light Chain
LTP	Tong-Term Potentiation
MAA	Marketing Authorisation Application
mAb	Monoclonal Antibody
mAb158	murine immunoglobulin G2a homologue of lecanemab
MCB	Master Cell Bank
mg	milligram
min	minute
mL	millilitre
mM	millimolar
MMV	Mouse Minute Virus
MO	Major Objection
MoA	Mechanism Of Action
MRT	Mean Residence Time from zero time extrapolated to infinite time
NAb	neutralising antibody
NAS	New Active Substance
ng	Nanogram
NLT	Not Less Than
NMT	Not More Than
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OOS	Out Of Specification
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
SmPC	Summary of Product Characteristics

SPECT	single photon emission computed tomography
T1/2	half-life
TAMC	Total Aerobic Microbial Count
Tg	transgenic
Tg2576	transgenic mice expressing human APP with Swedish mutation
Tg-APPArcSwe	transgenic mice expressing human APP with Arctic and Swedish mutations
Tmax	Time of occurrence for maximum (peak) drug concentrations
µM or µmol/L	micromolar

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eisai GmbH submitted on 9 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Leqembi, through the centralised procedure falling within the Article 3(1) and point 1of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2021.

The applicant applied for the following indication: "*Lecanemab is indicated as a disease modifying treatment in adult patients with Mild Cognitive Impairment due to Alzheimer's disease and Mild Alzheimer's disease (Early Alzheimer's disease) (see section 5.1).*".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance lecanemab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
24 October 2013	EMEA/H/SAB/040/1/Q/2013/SME	David Brown
18 December 2014	EMEA/H/SAB/040/1/FU/1/QA/2014/SME	David Brown
19 December 2013	EMEA/H/SAH/021/1/2013/III	Luca Pani and Susan Morgan
15 November 2018	EMEA/H/SA/3401/1/FU/1/2018/III	Fernando de Andrés Trelles and Anja Schiel
15 October 2020	EMEA/H/SA/3401/1/FU/2/2020/III	André Elferink and Elina Rönnemaa
25 March 2022	EMA/SA/0000077368, EMA/SA/0000088736 (clarification)	Mario Miguel Coelho da Silva Rosa and André Elferink
23 June 2022	EMA/SA/0000087915, EMA/SA/0000099679 (clarification)	Elina Rönnemaa and Flora Musuamba Tshinanu

EMEA/H/SAB/040/1/Q/2013/SME*

The qualification advice pertained to the clinical development and validation approach to the 'Predementia Clinical Outcome assessment' as a single primary efficacy measure of the cognitive and/or cognitive plus functional domains in Alzheimer's disease including: advice on the high-level research approach for the pCOA, the patient population for the COA, and target labelling considerations

EMEA/H/SAB/040/1/FU/1/QA/2014/SME*

The follow up qualification advice pertained to the clinical development and validation approach of the Predementia Clinical Outcome Assessment Tool (pCOA) as a composite endpoint for use in clinical trials of Mild Cognitive Impairment including: concepts of interest (COI), the target population and endpoint, whether the concept of interest and context of use for this pCOA could support the proposed targeted labelling claim, the approach to establishing clinical meaningfulness to support ADCOMS, the plans for the literature review, and the potential for qualification.

** The qualification procedure applicant was the Critical Path Institute on behalf of the Coalition Against Major Diseases (CAMD). CAMD was developing a clinical outcome assessment measure for predementia Alzheimer's disease trials. Eisai was listed as 1 of 14 organizations representing the subset of CAMD member organizations that had joined together to work on the qualification of a pre-dementia clinical outcome assessment (pCOA) scale for patients with Alzheimer's disease (AD). This group was referred to as the pCOA Task Force.*

EMEA/H/SAH/021/1/2013/III

The marketing authorisation (MA) applicant received CHMP scientific advice on the non-clinical and clinical development of BAN2401 intended for the treatment of Alzheimer's disease (AD) which pertained to the following aspects:

Nonclinical:

The needs for carcinogenicity, reproductive or developmental toxicity studies, and the sufficiency of completed nonclinical studies.

Clinical:

Clarification of the target treatment population to encompass both Prodromal Alzheimer's disease and mild Alzheimer's disease dementia subpopulations, the existence of a continuum of disease severity, diagnostic criteria, and approach to show delay of disability or disease modification.

Proposals for a novel Alzheimer's disease clinical composite score (ADCOMS), acceptability of its use as a single clinical primary endpoint in a confirmatory trial along with appropriate biomarker support for pivotal efficacy and safety studies for disease modification in Prodromal AD and mild AD dementia, as well as the potential target effects size and period, and the need for additional validation data.

The potential for a Phase 2 trial to be supportive to a single traditional parallel-arm pivotal study and the need for demonstrating efficacy in both subpopulations separately.

EMEA/H/SA/3401/2/2016/I

The MA applicant received CHMP scientific advice on the quality development of BAN2401 for the treatment of mild cognitive impairment due to Alzheimer's disease and prodromal Alzheimer's disease which pertained to the following aspects:

Quality: strategy for testing and release of future active substance and finished product batches of BAN2401

EMEA/H/SA/3401/1/FU/1/2018/II

The MA applicant received CHMP scientific advice on the non-clinical and clinical development of BAN2401 intended as a disease modifying treatment for mild cognitive impairment due to Alzheimer's disease and mild AD dementia and which pertained to the following aspects:

Pre-clinical:

Sufficiency of the nonclinical pharmacology and toxicology evaluation

Clinical:

Whether available data could provide evidence that amyloid PET correlated with positive clinical findings could be an appropriate biomarker to support the amyloid hypothesis for disease modification in early AD.

Whether study data to date demonstrated modification of underlying disease pathophysiology in early AD (correlation of reduction in brain amyloid load via PET and slowing of clinical decline via ADCOMS, ADAS-cog, & CDR-SB)

Whether the ADCOMS endpoint could be considered an appropriate clinical outcome measure in an early AD population, or what other data would be required to qualify the use of ADCOMS as an appropriate clinical outcome measure.

Whether a conditional marketing authorisation could be feasible in the anticipated clinical safety database and clinical development to date.

The proposed design and patient population for the post-approval/phase 3 study in this context, the associated safety monitoring plan, the proposed Modelling and Simulation Plan for BAN2401.

EMEA/H/SA/3401/1/FU/2/2020/III

The MA applicant received CHMP scientific advice on the development of BAN2401 for treatment of intermediate or elevated brain amyloid from. The scientific advice pertained to the following non-clinical and clinical aspects:

Nonclinical:

Toxicology study to support the clinical development of the intended subcutaneous formulation

Clinical:

Patient selection criteria, endpoints and statistical analyses for studies A3 and A45; dose titration for the earlier study A3;

Selection of the PACC5 as a sensitive measure of clinically meaningful cognitive change in the A45 population; clinical significance of amyloid reduction, intermediate Aβ and of amyloid related imaging abnormalities (ARIA);

Definition of pre-clinical AD population and predictive value of amyloid PET reduction in such population.

EMA/SA/0000077368

The MA applicant received CHMP scientific advice on the development of lecanemab for the treatment of early Alzheimer's Disease (AD, mild cognitive impairment due to AD and mild AD dementia). The Scientific Advice pertained to the following clinical aspects:

Clinical:

Changes to Study 301 with a focus on consequential changes and potential labelling implications at the time of MAA; SAP amendments to incorporate the and proposed COVID-19 pandemic mitigations

EMA/SA/0000088736

The applicant received request and received a clarification from the SAWP on 20 June 2022 regarding the CHMP response in the scientific advice letter EMA/SA/0000077368.

EMA/SA/0000087915

The applicant received scientific advice on the development of lecanemab for the treatment of early Alzheimer's disease (mild cognitive impairment due to AD and mild AD dementia). The scientific advice pertained to the following aspects:

Clinical:

Approach to support a new route of administration including source of data, dose to be investigated for the new route of administration, administration sites, different container closure systems, safety database, population of the human factor validation study.

EMA/SA/0000099679:

The applicant received clarification from the SAWP on the 5 September 2022 regarding the CHMP response in the scientific advice EMA/SA/0000087915) regarding the size of the proposed SC safety database in the context of the overall safety database for lecanemab.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	9 January 2023
The procedure started on	26 January 2023
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	17 April 2023

The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	2 May 2023
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 May 2023
The applicant submitted the responses to the CHMP consolidated list of questions on	7 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	18 October 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	26 October 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	9 November 2023
The applicant submitted the responses to the CHMP list of outstanding issues on	19 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	8 March 2024
SAG experts were convened to address questions raised by the CHMP. This step was then annulled following the appellate judgement of the Court of Justice of the European Union in Case C-291/22 P.	11 March 2024
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	28 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	14 June 2024
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	17 June 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	25 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Leqembi on	25 July 2024
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	25 July 2024

1.7. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Jan Mueller-Berghaus

The applicant submitted written notice to the EMA, to request a re-examination of LEQEMBI CHMP opinion of 25 July 2024, on	2 August 2024
The applicant submitted the detailed grounds for the re-examination on	17 September 2024
The re-examination procedure started on	18 September 2024
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP and PRAC members on	18 October 2024
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP and PRAC members on	18 October 2024
The CHMP Rapporteurs circulated the CHMP Rapporteurs joint assessment report on the detailed grounds for re-examination to all CHMP and PRAC members on	1 November 2024
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	12 November 2024
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation on	14 November 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterised by insidious and progressive cognitive and functional decline. Patients go through a stage of mild cognitive impairment (MCI) and subsequently deteriorate into progressively severe dementia. AD is the most common cause of dementia among older adults and is ultimately fatal.

2.1.2. Epidemiology and risk factors

According to a US-based study, the prevalence of MCI is estimated around 8-10% for adults aged 60-69 years, 15% for adults aged 70-79%, and 25% for elderly aged 80-84 years (Peterson, Neurology 2018). The World Alzheimer Report states that in 2018 over 50 million people around the world had dementia. In the European population, the prevalence of AD is estimated at 5.05% (Niu et al., Neurology 2017).

According to the literature, the strongest risk factors for AD are advanced age and carrying at least one APOE ε4 allele. Moreover, women are more likely to develop Alzheimer's disease than are men, especially after the age of 80 years. Women are also more likely to have a higher tau load, despite having a similar amyloid β burden. In addition, cardiovascular risk factors and an unhealthy lifestyle have been associated with an increased risk of dementia. The Lancet Commission on Dementia Prevention estimated that 12 modifiable risk factors together account for roughly 40% of the worldwide risk of any type of dementia. These estimates illustrate that prevention by intervening on modifiable risk factors is of great relevance, even if most of the dementia burden cannot be prevented via a lifestyle-intervention approach. However, evidence suggests that vascular risk factors do not increase the risk of Alzheimer's disease pathology as measured by cerebrospinal fluid biomarkers or PET. This evidence implies that lifestyle and vascular risk factors contribute to dementia, but not via the Alzheimer's disease pathway (Scheltens et al., Alzheimer's disease, Lancet 2021).

2.1.3. Biologic features

According to the literature, the preclinical phase of Alzheimer's disease is the cellular phase. Alterations in neurons, microglia, and astroglia drive the insidious progression of the disease before cognitive impairment is observed. Neuro-inflammation, alterations in the vessels, ageing, and dysfunction of the glymphatic system act upstream or in parallel to accumulating amyloid β in this cellular disease landscape. Amyloid β induces, via an unknown pathway, the spread of tau pathology which is associated with the appearance of necroptosis markers in neurons displaying granulovacuolar degeneration (Scheltens et al., Alzheimer's disease, Lancet 2021).

The current understanding of the mechanisms involved in pathogenesis is summarised by Khan et al. (Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease, Current Neuropharmacology 2020), see Figure 1 below.

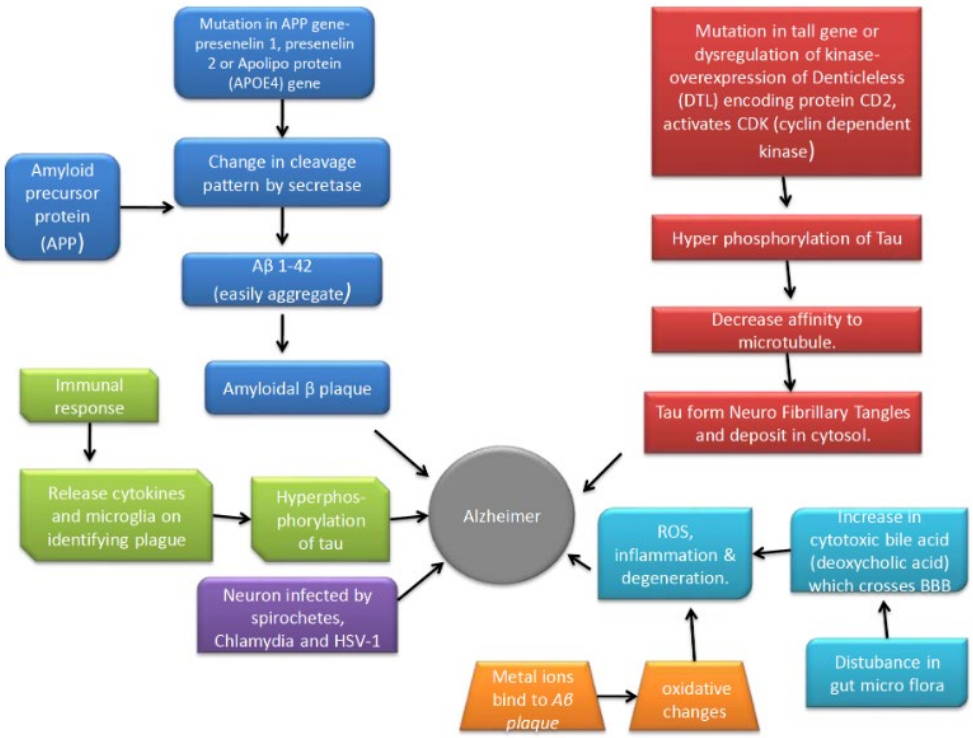


Figure 1. Mechanisms involved in pathogenesis of Alzheimer's disease (from Khan et al, 2020)

2.1.4. Clinical presentation, diagnosis and prognosis

Both the underlying pathophysiological process of AD and its clinical symptomatology are best conceptualised as a continuum: patients progress from normal cognition to MCI due to AD, followed by increasing severity of AD dementia (mild, moderate, and severe).

MCI due to AD is a pre-dementia phase of AD, characterised by the development of noticeable memory problems (amnestic) or impaired judgment or decision-making (non-amnestic), which does not affect independence of functional abilities, does not meet the criteria for dementia, and has AD as a suspected aetiology (Davis et al., Estimating Alzheimer's Disease Progression Rates from Normal Cognition Through Mild Cognitive Impairment and Stages of Dementia, Curr Alzheimer Res, 2018).

2.1.5. Management

Currently, pharmacological treatments approved in Europe (i.e. cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine) are targeted toward symptomatic therapy only.

Additionally, several studies (e.g. the Finnish FINGER study, the French MAPT study, the Dutch PreDIVA study) support that non-pharmacological treatment options including multimodal interventions and changes in lifestyles (e.g. healthy balanced nutrition, physical exercise, cognitive training and social activities, and vascular and metabolic risk management) can contribute to prevent cognitive decline and dementia.

There are no therapies approved that modify the course of the clinical disease progression at any stage of the disease.

2.2. About the product

Lecanemab, also known as BAN2401, is a humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody that binds with highest affinity to large soluble amyloid beta (Aβ) protein aggregates, known as protofibrils, while maintaining high affinity for fibrillar Aβ. Lecanemab is being proposed as a treatment for AD, with this submission, intended to support registration of lecanemab for the treatment of mild cognitive impairment (MCI) due to AD and mild AD, a population collectively described as early AD (EAD).

Lecanemab distinguishes itself from other anti-amyloid mAbs, in that it selectively targets large soluble protofibrils relative to monomers (greater than 1000-fold selectivity over Aβ monomers), with preferential activity over insoluble fibrils.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on insufficient strength of evidence, also in line of the criticalities of the dossier when evaluated in light of the applicable 'Points to consider on application with […] one pivotal study' (CPMP/EWP/2330/99).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 200 mg/2 mL or 500 mg/5 mL of lecanemab as active substance. Each mL of concentrate contains 100 mg of lecanemab.

Other ingredients are histidine, histidine hydrochloride monohydrate, arginine hydrochloride, polysorbate 80, water for injections.

The product is available in a 6 mL vial (Type I clear glass), with a stopper (chlorobutyl) and a seal (aluminium), with a dark grey flip-off cap for the 200 mg/2 mL presentation and with a white flip-off cap for the 500 mg/5 mL presentation.

2.4.2. Active substance

2.4.2.1. General information

Lecanemab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively binds to large soluble amyloid β (Aβ) aggregates (also termed protofibrils). Lecanemab selectively binds to Aβ protofibrils relative to monomers, while it also interacts with the insoluble fibrils that are a major component of amyloid plaque to either enhance clearance or neutralise toxicity towards neurons in the brain. The antibody consists of two heavy chains (HC; γ1-chains), each of 454 amino acids, and two light chains (LC; κ-chains), each of 219 amino acids. Each HC is glycosylated at Asn304, predominantly with core fucosylated biantennary structures with or without terminal galactose. The molecular weight of lecanemab is ~150 kDa, based on a sequence containing two lysine clipped HCs plus two G0F glycans.

The primary mechanism of action (MoA) is through antibody-dependent cellular phagocytosis (ADCP). However, other potential mechanisms of action are mentioned, such as binding to C1q and FcγRIIIa, associated with effector roles.

The applicant requested lecanemab to be considered as a new active substance (NAS). During the assessment, a major objection was raised concerning the applicant's justification of lecanemab NAS claim, requesting additional information about database searches performed by the applicant for structurally related substances in relation to the therapeutic moiety of the claimed NAS. The applicant has adequately addressed this issue and, therefore, lecanemab is to be qualified as a new active substance in itself as it was concluded that it is not a constituent of a medicinal product previously authorised within the European Union.

2.4.2.2. Manufacture, process controls and characterisation

The active substance is manufactured, tested and released in accordance with Good Manufacturing Practice (GMP).

Description of manufacturing process and process controls

The lecanemab active substance manufacturing process has been adequately described. Lecanemab is manufactured using a recombinant Chinese Hamster Ovary (CHO) cell line. Batch and scale definition is provided. One batch of lecanemab active substance derives from one vial of the Working Cell Bank (WCB). The main steps are thaw of one WCB vial, expansion of cells, inoculation of the production bioreactor, harvest, clarification, followed by downstream purification, including three chromatography, three dedicated viral clearance steps, ultrafiltration/diafiltration (UF/DF), concentration, formulation with polysorbate 80, filtration and dispensing into storage containers that are further stored at -40 ± 10°C. The final formulation is performed during the finished product manufacturing process.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The maximum number of cycles at each purification step has been mentioned in the description of the manufacturing process. Process hold-times have been defined, and their associated process controls are adequately described. Possibility of reprocessing is suggested in case of events related to the virus removal filtration step, the Single Pass Tangential Flow Filtration (SPTFF) step and the final active substance filtration step, linked to failure of post-use filter integrity test, re-concentration steps or upon technical failure of equipment. It is confirmed that no more than one reprocessing for each step will be considered and any reprocessing activities are included in the current hold periods for these steps. The overall approach is considered acceptable.

The lecanemab active substance is stored in ready to use single-use bioprocessing containers (10 L bags). The containers are sterilised by gamma irradiation (≥ 25 kGy) in line with Ph. Eur. 5.1.1 and ISO 11137. The product contact film is composed of ethylene vinyl acetate and the non-product contact layers are composed of ethylene vinyl alcohol/ethylene vinyl acetate. These materials comply with compendial requirements. Sufficient details on the active substance container closure system (CCS), including dimensions and technical drawings, are provided in the dossier. The applicant has evaluated the safety of the CCS by extractables studies using model solvents under temperature cycling conditions on representative 2 L bags and it was concluded that there are no substances which are required to be monitored in a migration (leachable) study.

In conclusion, the active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Both compendial and non-compendial raw materials are used in the manufacturing process. Specifications are provided for all non-compendial raw materials, including media components and feeds for cell culture, and chromatography resins used for purification. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

An Extended End of Production Cell Bank (EEPCB) was prepared. Genetic consistency was demonstrated for the MCB and WCB, as well as for the EEPCB. Future WCBs will be established according to a provided protocol which is deemed acceptable.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the lecanemab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Process parameters classification and in-process controls are justified based on process and product knowledge, risk assessments and experience with similar products and processes. Actions taken if limits are exceeded are also specified. The proposed acceptable ranges and acceptance criteria/action limits established respectively for process parameters and process controls are justified based on manufacturing process development and process characterisation studies. Analytical methods used for control of critical in-process controls and their validation/qualification, as applicable, are also documented.

Process validation

The process performance qualification (PPQ) of the lecanemab active substance manufacturing process was performed at the proposed commercial site. Commercial Process C-2 batches originating from four independent thaws were manufactured in the PPQ campaign. Overall, the approach taken for validation is considered acceptable. Deviations observed during the process validation studies were discussed and it was concluded that they have no impact on the validity of the studies and/or product quality. Ongoing process verification activities will be performed to provide ongoing assurance that the manufacturing process remains in a state of control during commercial manufacture.

Reprocessing of filtration steps has been validated by using a scale-down model. The applicant claimed that validation of the reprocessing step at full-scale will be performed as per a pre-defined protocol in the event that reprocessing of a batch is required during routine production, which is acceptable.

Process-related impurities are removed in a consistent manner by the downstream purification process, achieving levels below the safety concern values. Clearance studies were performed for the following process-related impurities: residual host-cell protein (HCP), host cell deoxyribose nucleic acid (DNA), Antifoam Q, lauryldimethylamine-N-oxide, Protein A leachate, Poloxamer 188 and γ-aminobutyric acid.

The column lifetimes as defined for the commercial manufacturing process have been validated by using a scaled-down model. The proposed resin reuse cycles are concurrently verified at manufacturing scale, which is considered acceptable. Appropriate information was provided regarding the cleaning of the columns.

The lecanemab manufacturing process includes reusable membranes at the UF/DF and SPTFF steps. The Applicant stated that the maximum lifetime for the membranes re-use is not defined since their suitability is checked prior to each commercial run by pre-defined criteria. This approach is acceptable.

Hold-time validation studies were performed to support the possible hold-times defined for routine production. Use of small-scale containers for biochemical stability study is acceptable. Microbial stability studies were performed in the commercial scale product pool vessels using growth promoting surrogate medium.

A risk-assessment to evaluate potential extractables/leachables from equipment used during the manufacturing process of the active substance was performed and demonstrated that no risk to product safety and quality is foreseen from the use of the equipment/materials involved in the lecanemab manufacturing process.

Summary of shipping validation for active substance is provided and is acceptable**.**

In conclusion, the active substance manufacturing process can be considered adequately validated, ensuring that active substance of reproducible quality can be consistently produced.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development programme. Four manufacturing processes were identified during development: process A-1, B-1, C-1 and C-2. Several changes were introduced during process development, most notably change of the manufacturing site, increase of the manufacturing scale, change in the formulation and increase of active substance concentration, cell culture and purification process optimisation, change in the storage conditions of the active substance (including decrease/increase in the container size).

The finished product batches used in the Phase 3 pivotal clinical trial (Protocol 301) and its open-label extension were produced using either lecanemab active substance manufactured via Process B-1 or Process C-1, while none of the finished product batches produced with lecanemab manufactured using Process C-2 have been assigned to a clinical trial. During the assessment, a major objection was raised with regards to the proposed strategy applied by the applicant to demonstrate comparability of the active substance processes which was not deemed in accordance with ICH Q5E. In response, the applicant revised the concerned section of the dossier and provided additional justification to address the major objection raised, which allowed for an assessment of the representativeness of the proposed commercial process C-2 versus the Processes B-1 and C-1. Based on the overall data provided, the active substance manufacturing process was demonstrated to be comparable throughout development.

Characterisation

The lecanemab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. The process-related impurities were sufficiently documented as described during the process validation studies.

In conclusion, the characterisation is considered appropriate for this type of molecule.

2.4.2.3. Specification

The release and stability specification for lecanemab active substance are set based on regulatory guidelines, analytical capability, process capability and clinical experience.

During the assessment, the applicant was requested to tighten the acceptance criteria for several quality. The limits for stated impurities are supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies.

Overall, the parameters included in the release and shelf-life specification are found adequate to control the quality of lecanemab active substance.

Analytical methods

Method descriptions for all non-compendial analytical procedures are provided and validation is performed according to ICH Q2. The compendial methods have been verified to demonstrate suitability for the intended purpose.

Batch analysis

Batch analyses data have been provided for commercial process C-2 active substance batches and process C-1 batches. In addition, supportive release data for Process A-1 active substance batches and Process B-1 active substance batches are presented. All results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

A two-tiered reference standard system is in place, with a primary reference standard (PRS) and a working reference standard (WRS) prepared using the proposed commercial process C-2. The WRS is used as the product reference standard for release and stability testing of the active substance/finished product. The WRS may also be used for other purposes, including as a reference comparator for characterisation. The PRS and WRS are placed on stability and tested annually per provided stability protocol. The qualification protocol for the current reference standards is satisfactory. All future reference standards will be prepared according to the proposed protocol.

2.4.2.4. Stability

The proposed shelf-life for the lecanemab active substance is 24 months when stored at ≤ -40°C in the defined CCS.

The applicant carried out stability studies on PPQ batches from commercial Process C-2 and registration Process C-1 batches (considered representative of the commercial process), in accordance with ICH guidelines. The container used during the stability studies is considered representative of the commercial CCS in terms of material of construction, closure and worst-case fill volume. The parameters tested include the physicochemical and general assays and tests for determination of the protein concentration, biological activity and size and charge heterogeneity, with the same limits applied as for release testing.

Long-term stability data were provided. Additionally, up to 12 months stability data under accelerated conditions (5 ± 3°C) and up to 6 months stability data under stressed conditions (25 ± 2°C / 60 ± 5% RH), from both registration and PPQ active substance batches, were included in the dossier. Supportive stability data from registration and PPQ batch at intermediate conditions (-20°C) for up to 6 months were also provided.

Under long-term storage conditions, all tested quality attributes for all batches met specification, except for the results for clarity reported for the registration process C-1 batches and only at the 3-month stability time point. An investigation was performed to evaluate the probable causes. The investigation root-cause was inconclusive, however, as a result, updates were made to the method for reagent preparation/storage and sample handling/observation. Results at the 6-month time point were within specification, therefore, the out-of-specification (OOS) result at 3 months was determined not to be attributed to the storage condition.

Based on the provided stability data that show no negative trend over the test period and based on the demonstrated comparability between C-1 and C-2 batches, the stability results indicate that the active substance is sufficiently stable and justify the proposed shelf-life in the proposed container.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as concentrate for solution for infusion containing 200 mg/2 mL or 500 mg/5 mL of lecanemab as active substance. The finished product is manufactured in two homothetic presentations differing only with regards to the filling volume. Each mL of concentrate for solution for infusion is a preservative-free solution containing 100 mg of lecanemab, histidine, histidine hydrochloride monohydrate, arginine hydrochloride and polysorbate 80 at pH 5.0. The concentrate is a clear to slightly opalescent, colourless to pale yellow solution, intended for intravenous infusion following dilution, as single use only. To ensure that the entire product volume can be extracted from the vial, an overfill of 0.25 mL or 0.30 mL is applied to the 2 mL presentation or 5 mL presentation, respectively. No overages are applied for the finished product formulation.

All excipients used in the formulation of lecanemab finished product are of Ph. Eur. compendial grade and representative certificates of analysis for each excipient have been provided. No novel excipients and no excipients of human or animal origin are used in the finished product formulation. Compatibility between the excipients and the lecanemab active substance is considered demonstrated by the long-term stability data. In summary, the excipients used are considered acceptable.

The commercial formulation of the finished product was established in formulation screening and robustness studies. The objective of the finished product formulation development programme was to develop a formulation sufficiently stable and robust for manufacturing, storage, transportation and administration of lecanemab by intravenous infusion.

The primary packaging is a 6 mL vial (Type I clear glass), with a stopper (chlorobutyl) and a seal (aluminium), with a dark grey flip-off cap for the 200 mg/2mL presentation and with a white flip-off cap for the 500 mg/5 mL presentation. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Extractable studies were performed for the individual primary container closure using the 2 mL finished product presentation as worst-case and no safety concerns were identified.

Compatibility testing and in-use stability testing were performed by diluting the finished product to target concentrations. The finished product batches used to perform the in-use compatibility study are representative of the commercial processes. Different infusion bag and infusion kit material types were used in the in-use compatibility assessment. All prepared test samples were held for 24 hours in their infusion bags at ambient temperature under normal indoor lighting conditions and tested for physico-chemical attributes during the in-use stability study. OOS results were observed for visible particles test parameter, which were adequately described and justified by the applicant as environmental contamination. In addition, appropriate corrective actions/preventive actions (CAPAs) are set in place by the applicant to mitigate any risk of extrinsic particulate contamination. Also, the risk of potential phthalate extraction is discussed and no risk of exposure upon lecanemab administration is expected.

Therefore, it is endorsed that the chemical and physical in-use stability of lecanemab finished product when diluted and stored in intravenous infusion containers has been demonstrated for up to 24 hours

at ambient temperature (15°C - 25°C), under lighting conditions representative of a hospital or clinical setting.

2.4.3.2. Manufacture of the product and process controls

The manufacture, control, packaging and release of lecanemab finished product is performed, in accordance with GMP.

During the assessment, a major objection was raised requesting retesting upon EU importation for the finished product, as per provisions of Article 51 of the Directive 2011/83/EC. In response, the applicant has updated the proposed manufacturing flowcharts (Annex 5.8) for lecanemab active substance and finished product to address this requirement and confirmed that all test methods have been successfully transferred to the EU batch release testing sites. The major objection is considered resolved.

Over the course of manufacturing process development, the manufacturing process has undergone several major changes: change in the manufacturing site, batch size, manufacturing process steps, container closure system size, qualitative and quantitative formulation of the finished product. In total, four processes were used throughout development of lecanemab finished product: FL-1, FL-2, FL-3 and FL-. The proposed commercial finished product manufacturing processes are FL-3 and FL-4.

By considering the manufacturing development of both the active substance and the finished product, the manufacturing processes used during the development of lecanemab product are Process A-1:FL-1, Process B-1:FL-2, Process C-1:FL-2, Process C-2:FL-3 and Process C-2:FL-4. Most of the finished product batches used during the Phase 3 clinical studies were manufactured by Process B-1:FL-2, while finished product clinical batches were manufactured by Process C-1:FL-2.

The strategy regarding the choice of batches used during the comparability studies was discussed by the applicant. However, similarly to the deficiencies identified for the active substance comparability studies, during the assessment a major objection was raised with regards to the proposed strategy applied by the applicant to demonstrate comparability of the finished product processes. In response, the applicant updated the comparability data in accordance with ICH Q5E and the provided data are now considered sufficient to support the conclusion that different finished product manufacturing processes and formulations used throughout clinical development were comparable and that these changes did not have a significant influence on the quality of the product. The major objection is considered resolved.

The finished product proposed for commercialisation is manufactured at both sites following the same overall standard process covering thawing, pooling and dilution of the lecanemab active substance with the formulation buffer, bioburden reduction filtration, sterile filtration, aseptic filling and visual inspection. However, different scales are used between the two manufacturers.

In addition, several other differences between the two manufacturing sites are noted, which are considered by the applicant to be technical adaptations due to facility fit/increase of the batch size. An overview of the finished product manufacturing process flow diagram at both sites is provided.

Product critical quality attributes (CQAs) were identified using a product risk assessment. Process risk assessments were conducted for the manufacturing process used at each site. The outcome of these risk assessments, together with data from process characterisation studies, were used to establish the final set of process controls (i.e. input controlled parameters and output in-process tests and controls) for the commercial manufacturing operations.

An extensive side-by-side comparison between the two processes at each manufacturing site, including the control strategy (process parameters and process controls) is provided, which demonstrate that both processes are capable of producing the finished product of comparable quality.

Hold-times are also different between the two processes and supported by validation data, which is acceptable. In addition, reprocessing is only proposed for the process at one site at the bioburden reduction filtration step, where a re-filtration can be considered through a second bioburden filter into a second holding vessel, in case of an assignable cause (e.g. equipment failure). Refiltration will not be performed to correct bioburden excursions and is limited to one occurrence for each finished product batch. This proposal is found acceptable.

In summary, the manufacturing process development strategy is described in detail. The proposed control strategy is considered to be in line with process characterisation studies and supported by validation data. The provided justifications for criticality classification of in-process parameters and the proposed criteria for the chosen limits are considered appropriate.

The manufacturing process has been validated, by successful completion of consecutive PPQ batches (for each dose presentation), in accordance with a pre-defined protocol. Deviations were explained and justified. Process validation results demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The shipping process from the finished product manufacturing sites to the packaging site has been qualified by simulated shipping studies to demonstrate maintenance of temperature control, to ensure that the transport packaging protects the product from shipping hazards and to confirm that potential mechanical stresses from shipping do not impact product quality. The transport qualification is considered appropriate.

2.4.3.3. Product specification

During the assessment, the applicant was requested to tighten the acceptance criteria for several quality attributes.

No additional process or product-related impurities are introduced or expected to form as a result of the finished product manufacturing. Therefore, finished product impurities are expected to be the same as those described in the active substance section.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. In addition, the risk of extractable/leachables and elemental impurities is found sufficiently addressed and no additional control measures are necessary at the finished product level.

Overall, the selection of specification attributes and setting of the acceptance criteria are in line with ICH Q6B and are found adequate to control the quality of lecanemab finished product at release and during shelf-life.

Analytical methods

Compendial and non-compendial methods are used for testing of lecanemab finished product. Description and validation, in accordance with ICH guidelines, of the analytical methods specific for the finished product (sterility, endotoxin and CCIT) are provided. Other methods are either compendial or identical to those used for the active substance.

Batch analysis

Batch analysis data were provided for process C-1:FL-2 clinical finished product batches, for process C-2:FL-3 finished product batches (including commercial PPQ batches) and for commercial PPQ process C-2:FL-4 finished product batches, covering both 2 mL and 5 mL presentations. The results are within the specifications and confirm consistency of the manufacturing process. Supportive batch analysis data are also provided for process A-1:FL-2 finished product batches and for process B-1:FL-2 finished product batches that were used in stability studies and/or clinical studies.

Reference materials

Reference is made to the corresponding active substance section.

2.4.3.4. Stability of the product

The applicant claimed a shelf-life for the finished product of 24 months when stored at 2°C to 8°C in the defined CCS.

To support this shelf-life claim, process C-2:FL-3 PPQ batches (for each of the 2 mL and 5 mL presentations), process C-1:FL-2 registration batches (batches for each of the 2 mL and 5 mL presentations) and clinical process C-2:FL-3 batch (5 mL presentation), were all placed on stability. Additionally, process C-2:FL-4 PPQ batches (for each of the 2 mL and 5 mL presentations) produced at the second finished product manufacturing site, have also been placed on stability. Stability studies are performed in accordance with the ICH guidelines, using the commercially proposed CCS.

Moreover, freeze-thaw (–80°C freeze/2-8 °C) and photostability testing were conducted on finished product batches representative of the commercial 2 mL and 5 mL fills, as part of the finished product formulation development studies.

The same parameters and limits are applied during shelf-life of the finished product as for release, except for osmolality, extractable volume, identity and bacterial endotoxins, which are tested only at release, and for container closure integrity testing (CCIT), which is only performed during stability.

Stability results for lecanemab finished product stored under recommended long-term conditions (5°C ± 3°C) are provided. In addition, results under accelerated conditions (25°C ± 2°C, 60% ± 5% RH) and under stressed conditions (40 ± 2°C/75 ± 5% RH) for up to 6 months for C-1:FL-2, C-2:FL-3 and C-2:FL-4 batches.

Test results after three freeze-thaw cycles show no product quality changes, demonstrating that the finished product is robust to freeze-thaw stress. Photostability data for lecanemab show that, when exposed to ICH Q1B exposure limits, the finished product in unlabelled (nude) vials undergoes multiple changes to product quality, however no product quality changes were seen for foil wrapped dark controls and for the finished product vials packaged into cardboard cartons representative of commercial secondary packaging.

Based on the provided stability data that show no negative trend over the test period under long-term storage conditions and based on the demonstrated comparability between batches manufactured at the two commercial manufacturing sites (C-2:FL-3 and C-2:FL-4), the stability results indicate that the

finished product is sufficiently stable and justify the proposed shelf-life of 24 months at 2°C to 8°C in the commercial container. Moreover, as discussed in the Pharmaceutical development section, in-use stability of the diluted finished product solution has been demonstrated for 24 hours at temperatures up to 25°C.

The applicant commits to conduct and complete the ongoing stability studies, which includes stability studies for process validation batches, according to the stability protocols. This approach is endorsed.

2.4.3.5. Adventitious agents

A comprehensive strategy, including raw material sourcing and testing, in-process testing, viral clearance process validation and facility controls, is used to ensure that the lecanemab active substance and finished product are free of adventitious agents. The strategy is designed in accordance with ICH Q5A, ICH Q5D and ICH Q6B.

No raw materials of animal or human origin are used in the manufacture of the MCB, WCB, active substance or finished product. Several materials of biological origin are used in the commercial manufacturing process and adequate details on the source, origin and control of these materials for potential adventitious agents are provided in the dossier.

Cell banks were controlled for viral contamination and original virological control reports are provided. The data resulting from extensive experimental studies on the MCB, WCB and EEPCB cells do not reveal any viral contamination of these cell banks. During the passage history of the cell line, New Zealand-sourced and US-sourced fetal bovine sera were used. It is declared that this host cell bank was tested and found to be negative for the presence of adventitious viruses. During early development of the cell line, a single lot of recombinant (yeast expressed) human albumin was utilised in the development of the pre-MCB. This material was subsequently eliminated from the MCB.

Routine in-process tests are in place to ensure that the active substance and finished product processes remain free from microbial contamination and endogenous adventitious agents. These controls include tests for presence of bacteria, fungi, mycoplasma and a broad-spectrum of viruses using an *in vitro* assay for adventitious viruses. In addition to the routine controls and testing for bacteria, fungi and mycoplasma, routine testing of the unprocessed bulk harvest (UBH) for viruses is performed. UBH samples are collected from the production bioreactor at the end of cell culture and stored under the appropriate conditions until testing. UBH from all batches manufactured to date was free from detectable virus.

The capacity of the commercial finished product manufacturing process to remove or inactivate viruses was assessed as part of the overall adventitious agents safety risk assessment strategy. A qualified scaled-down version of specific steps of the purification process known to remove/inactivate virus was challenged with known amounts of model viruses. These studies demonstrated robust removal of potential viruses by the manufacturing process.

Overall, sufficient information has been provided, and no risks have been identified with regards to viral/TSE safety.

2.4.3.6. GMO

Not applicable

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During assessment, major objections were raised on quality grounds concerning: incomplete justification of the lecanemab new active substance claim; the proposed strategy applied by the applicant to demonstrate comparability of the active substance and finished product processes, which were not deemed in accordance with ICH Q5E; insufficient evidence to demonstrate that the Aβ binding assay and the FcγRIIa binding assay are representative of the claimed biological activity of lecanemab; the need for retesting upon EU importation for the finished product, as per provisions of Article 51 of the Directive 2011/83/EC. The major objections, as well as all the other concerns raised throughout the procedure, have been satisfactorily resolved.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the benefit/risk ratio of the product (see Recommendation below).

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

A comprehensive package of *in vitro* and *in vivo* studies was designed to characterise the pharmacological properties of lecanemab, a humanised immunoglobulin G (IgG)1 monoclonal antibody (mAb) with respect to its mechanism of action consisting in targeting amyloid-β (Aβ), pharmacokinetics (PK), pharmacodynamics, and toxicological profile. Studies were performed using either lecanemab, or the surrogate murine mAb (mAb158), or an allotype-variant murine homologous recombinant protein of mAb158 (rec158). The nonclinical safety testing strategy for lecanemab relied on the ICHS6 guideline. The toxicity programme of lecanemab relied on intravenous toxicity studies, *i.e.*, single-dose in rats (GLP) and monkeys (non-GLP), and 4- and 39-week repeated-dose intravenous GLP toxicity studies in monkeys. Subcutaneous local tolerance (GLP) study was also performed in monkeys. *In vitro* tissue cross-reactivity of lecanemab was evaluated using a full panel of fresh-frozen rat, cynomolgus monkey, and human tissues (GLP). Alternatively, evaluation of cerebral microhaemorrhage potential was conducted within the pharmacology studies in Tg2576 and Tg-APPArcSwe using mAb158. A weight-of-evidence assessment of carcinogenicity risk was conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Lecanemab and mAb158 antibodies behave similarly in their interactions with Aβ monomers and Aβ protofibrils when analysed by ELISA or surface plasmon resonance (SPR) (lecanemab, KD = 3.3 μM; ka = 3.8×104 1/Ms), and displayed a >200-fold higher affinity for Aβ protofibrils compared to Aβ monomers. Binding affinity of mAb158 was large Aβ protofibrils > 6-mer > 3-mer of Aβ oligomers. Sensorgrams showed the Aβ monomer dissociates rapidly from lecanemab and mAb158, while both antibodies show a slow dissociation from the Aβ protofibril. Binding affinity of Aβ(1-42) protofibrils to lecanemab was 7500-fold higher than that of Aβ(1-40) monomer. These data suggest that lecanemab has higher affinity and specificity for Aβ protofibrils, compared with Aβ monomer. Combined ELISA and X-ray crystal structures of lecanemab Fab fragment with Aβ peptide (Aβ(1-9)) peptide showed peptide bound to one of the two Fab fragments in the asymmetric unit, and the interaction between mAb158/lecanemab and Aβ protofibrils was dependent on the dual effect of the 2 linked Fab fragments in the shape of F(ab')2. Hydrogen deuterium exchange-mass spectrometry confirmed and further suggested lecanemab recognised a conformational epitope consisting of the N-terminal and mid regions on Aβ(1-42) protofibrils. Biolayer interferometry confirmed that lecanemab binds to the first 3 amino terminal amino acids. Both mAb158 and lecanemab inhibited β-sheet aggregates formation.

The affinity and selectivity of lecanemab for Aβ species were compared to antibody analogues using SPR, inhibition ELISA and immunoprecipitation approaches. Lecanemab showed the highest affinity and strongest preference for the soluble Aβ protofibrils versus monomeric and fibrillar forms of Aβ in comparison with the other Aβ targeting antibodies. In a further study aiming at comparing the binding efficiency of lecanemab with aducanumab and gantenerumab to soluble Aβ protofibrils extracted from brains of human AD brain, lecanemab bound to Aβ protofibrils with a 12.4 to 26.1-fold higher efficiency as compared to aducanumab when plotting antibody-response curves of efficiency to immunodeplete Aβ protofibrils, but similar binding efficiency as Gantenerumab.

Using biolayer interferometry and SPR, binding of lecanemab to human FcγRI and FcγRIII (known to be involved in Antibody-Dependent Cellular Phagocytosis (ADCP) was demonstrated, but not to FcγRII. While in a similar range of KD values as for IgGs, affinity of lecanemab is higher for FcγRI than FcγRIII.

Whether Aβ clearance after lecanemab treatment may be protective, was investigated through assessment of its effect on Aβ protofibril-induced neuronal cell toxicity, and on Aβ oligomer-induced long-term potentiation (LTP) impairment in hippocampal slices. Viability assays showed lecanemab displayed a neuroprotective potential in primary cortical chicken neurons and human neuroblastoma cells at a concentration of 1-3μM in presence of Aβ-42 (1μM). Both mAb158 (≥100 μg/mL) and lecanemab (100 and 300 μg/mL) inhibited significantly Aβ1-42 protofibrils (3 μM)-induced neuronal toxicity *in vitro* in cultured rat primary medial septum neurons. Lecanemab (0.02 μM) demonstrated the ability to rescue Aβ (1μM)-induced LTP impairment but had no effect on LTP when used alone. This rescue of LTP impairment appears dose dependent since lower concentration of lecanemab (0.002 μM) did not demonstrate a protective effect against Aβ1-42 induced LTP impairment. As lecanemab is able to reverse the deficit in LTP produced by Aβ, improvement of synaptic activity is expected.

The applicant conducted a plethora of studies investigating the effects of short-term and long-term administration of mAb158 or rec158 on Aβ-protofibril levels using 3 recognised models of AD mice, aged of 4 to 20 months (Tg2576), 9 to 24 months (Tg-APPArcSwe) or 26–27 weeks (AppNL-G-F knock-in mice) at time of initiation of treatment, once weekly intraperitoneally up to 18 weeks. Despite difference in time course of AD stigmates, *in vivo* pharmacodynamics effects, *i.e.* decrease in

Aβ-protofibrils content, was achieved in Tg2576, Tg-APPArcSwe, and APPNL-G-F mice at concentration compatible with the human exposure at the clinical dose (plasma exposure of mAb158 estimated 244-466 µg/ml and 29,154-81,692 ng·h/mL in Tg mice versus human exposure of 307 µg·h/mL and 37,700 µg·h/mL at the clinical dose of 10 mg/kg every 2 weeks).

In Tg2576 mice, mAb158-mediated effects on amyloid forms were more prominent in long term studies rather short-term studies, and in oldest mice.

When plasma concentrations were available in these studies, decrease of protofibrils level and plaques were observed at AUC of 29,154-81,692 ng·h/mL in Tg2576 mice, suggesting effective Aβ targeting should be reached at the clinical dose of 10 mg/kg every 2 weeks (AUC0-t of 37,700 µg·h/mL and Cmax of 307 µg/mL) in humans.

The potential for reduction of Aβ protofibril levels mice was demonstrated with mAb158 with short and long-term treatment in Tg-APPArcSwe.

Finally, mAb158 (10 and 30 mg/kg) once a week for 16 weeks significantly reduced Aβ protofibrils, insoluble Aβ levels and Aβ plaques in brains of AppNL-G-F knock-in mice aged 26–27 weeks old.

Given the lack of cognitive improvement in the fear conditioning assays in these models and no data from other relevant behavioural tests, there is no proof supportive for cognitive improvement in any mice strains.

Deficits in regional perfusion in the tempo-parietal regions of the brain are associated with mild cognitive-impairment, dementia, and AD in humans. As a consequence, whether brain function was improved was investigated after 12 weeks-mAb158 (50 mg/kg/week) treatment through neuroimaging measure of cerebral perfusion, glucose metabolism, and neuronal viability in the 19 months-old Tg2576 mice. In a few animals, immunohistochemistry showed reduction in plaque load in treated mice when compared to untreated mice in the hippocampus (7-18%) and cortex (9-25%) with a possible preferential effect on diffuse versus core plaque concomitantly with both an increase in blood flow in the cortex and hippocampus, an improved neuronal viability, but there was no benefit on glucose utilisation.

2.5.2.2. Secondary pharmacodynamic studies

Thrombospondin-1 was identified to bind lecanemab with low affinity (KD≈4µmol/L) in rat, mouse, monkey, human control, and human AD plasma. Competitive study suggested that Aβ and Thrombospondin-1 compete for the same binding site on lecanemab. Human plasma concentration was estimated 1000-fold lower than lecanemab (predicted Cmax at steady state is 280.5 µg/mL at 10 mg/kg bi-weekly), therefore off-target effect is considered unlikely.

Based on combined studies with lecanemab (or mab158) profiled on ProtoArray Human Protein Microarrays and immunoprecipitation studies, comparative investigation of lecanemab's partners in AD plasma versus monkey plasma did not supported differences, and four putative partners were identified. Fibrinogen chains were identified to indirectly bind to lecanemab through interaction with amyloid aggregate forms, but no safety concern as clotting disorders were observed from clinical studies and non-clinical toxicology studies. Regarding lecanemab's binding to the pain-related opioid peptide Proenkephalin, direct interaction with lecanemab cannot be ruled out as the protein was not present in the targets of the ProtoArray chips assay. However, there are no report linking Proenkephalin A interaction with Aβ species, off-target seems unlikely. Similarly, the binding to amyloid A4 may also be considered reasonably without safety concern as targeting of A4 protein in pathological conditions would be favourable. Although lecanemab binding to C1q was concluded at least indirectly mediated through amyloid forms, direct C1q binding lecanemab cannot be ruled out.

While a functional Complement-Dependent Cytotoxicity (CDC) assay was not conducted, and there is no evidence lecanemab has abrogated CDC potential compared to human IgG1 as its structures is not mutated in the Fc area specific for binding of C1q, there are some factors to derisk: (i) complement activity has been attributed to elevated avidity of the IgG hexamer for the six-headed globular C1q protein, then lecanemab targeting of soluble forms of amyloid may not favour lecanemab-C1q complexes as when targeting membrane antigens, to lead to complement activation and deposition of C3b to further opsonise the target, subsequent activation of C1q, leading to deposition of C3b to further opsonise the target, but also to the formation of the membrane attack complex, C5-C9, causing disruption of the targeted membrane; (ii) no evident safety concern were raised from clinical studies in humans and/or in clinical species during toxicology studies in term of anaphylatoxin/complement activation-related pro-inflammatory products, sepsis or immune effects, complement-mediated RBC lysis with release of RBC constituents, or leucopenia. Altogether these likely suggest low safety concern for complement activation pathway while formal CDC assay was not performed. It is known IgG1 has also the highest affinity among immunoglobulins to all FcγRs, leading to significant effector functions. Given structure was not modified by directed mutations, and lecanemab was proven to bind FcγRI/IIIa in binding assays it is expected lecanemab would retain potential for Antibody Dependent-Cellular Cytotoxicity (ADCC). Given the mechanism of action of lecanemab that is binding of the soluble Aβ species rather than potential targeting of membrane antigen, recruitment of Natural Killer cells or macrophages seems unlikely to elicit cell-mediated cytotoxicity. In addition, there were no report on elevated level for activating cytokines in animals and human studies, or any indication of T cell activation. Both Applicant' discussion and the lack of findings at non-clinical and clinical level are sufficient to support that lecanemab is unlikely to raise ADCC- or CDC-related concern. Immunogenicity risk of lecanemab was derisked through *in silico* approaches, EpiScreen™ assay, and also from lack of finding from repeat-dose toxicity studies.

2.5.2.3. Safety pharmacology programme

In accordance with ICH guidelines S6(R1) and S7A no stand-alone safety pharmacology studies were performed. The effect of lecanemab on the cardiovascular system, CNS, and respiratory system was evaluated in the 4-week GLP repeated-dose toxicity study in cynomolgus monkeys. Lecanemab (5, 15, or 50 mg/kg) was administered intravenously once a week for 4 weeks to male and female cynomolgus monkeys. There were no test article-related adverse effects on CNS, cardiovascular system, or respiratory function at any doses up to 50 mg/kg, which was a maximum feasible dose based on injection volume for slow bolus administration in monkeys. Based on the results, the NOAEL was considered to be 50 mg/kg with mean AUC(0-384h) for males and females were 93,000/228,500 µg·h/mL, and mean C5min were 1290 /2305 µg/mL for males and females on Day 1 / 29. Based on a human steady state AUC0-t of 37,700 µg·h/mL and Cmax of 307 µg/mL at the clinical dose of 10 mg/kg every 2 weeks multiple of exposure for Day 1/29 relative to the exposure at the clinical dose are 2.5/6 (AUC) and 4.2/7.5 (Cmax), respectively. No potential risk to the cardiovascular system (ECG monitoring) was observed in monkeys during the 39-week GLP repeat-dose study.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted with lecanemab.

2.5.3. Pharmacokinetics

2.5.3.1. Methods

Regarding the validated enzyme-linked immunosorbent assay (ELISA) methods used to support the toxicokinetic or pharmacokinetic evaluations, mainly mAb158 in murine plasma and dilution buffer (for CSF), lecanemab in the serum of toxicological species (monkey), validation method studies included calibration curve, specificity, prozone effect, recovery, intra- and inter-assay variations, limit of quantification, dilution reproducibility/linearity and storage stability under frozen condition and in freezing/thawing cycles incorporating short-term room temperature stability. The results met the acceptance criteria supporting the ELISA methods were fully adequate for the quantitation of mAb158 in mouse plasma, and lecanemab in monkey serum. Quantitation range of lecanemab was established in rat serum, but no complete validation process and stability were achieved, but the method was only used for a non-pivotal single toxicity study in rats. An ELISA method was adequately validated for mAb158 to reliably quantify the concentration of mAb158 in mouse CSF. An ELISA method was capable of quantification levels of anti-lecanemab in monkey serum. Alternatively, an electrochemiluminescence method was also successfully validated for the determination of anti-lecanemab antibody in cynomolgus monkey serum. Drug tolerance was determined in the presence of lecanemab. However, the results from one of single-dose pharmacokinetic study of lecanemab and rec158 antibodies in Tg-APP ArcSwe and non-transgenic mice (Study AD-TR-059) must be interpreted with caution considering the technical weaknesses (associated with the non-GLP conduct of the *in-life* part and quantitation using non-validated ELISAs). Similarly, bio-analytical methods for determination of antibody concentration with non-GLP blood partitioning/plasma protein binding studies were not considered fully validated. The lack of GLP compliance during the validation of the two bioanalytical methods used for detection of the anti-lecanemab antibodies and lecanemab in the 4- and 39-week pivotal toxicology studies in monkeys had been considered having no impact on the quality of the data generated A single photon emission computed tomography (SPECT/CT imaging) was applied to quantify the *in vivo* uptake, distribution, and time profile of ^{125}I-rec158 in peripheral organs and brain by and *ex vivo* gamma counting in aged Tg2576 mice (which overexpress human Aβ) and non-transgenic mice as controls are considered to satisfy to state-of-art.

2.5.3.2. Single dose studies with lecanemab and surrogate antibodies

The plasma Cmax and AUC0-168h values of mAb158 increased in a dose-proportional manner between 1 and 5 mg/kg and increased in a less than dose-proportional manner between 5 and 15 mg/kg in female Tg2576 mice. The CSF concentration peaked at 24 to 72h at dose of 1, 5 and 15 mg/kg. T1/2 values were 69.70, 104.74 and 56.04h for 1, 5 and 15 mg/kg, respectively. CSF-to-plasma ratios were 0.53, 0.44 and 0.30% at 1, 5 and 15 mg/kg based on AUC0-168h, respectively. These results suggest brain penetration of the mAb158 in Tg mice. However, inconsistencies in estimation of Tmax, Cmax and half-lives values may have occurred due to large variability or concentration below the concentration quantification limit at given time points post-dose in this single-dose pharmacokinetics study. Lecanemab exhibited a short T1/2 in plasma/CSF/brain homogenates of both Tg2576 (1.4/1.4/3.5 days) and non-Tg (1.6/2.5/1.8 days) mice after single intraperitoneal dose. The half-life was 2.5 times longer in brain of Tg mice compared to plasma. Similarly, rec158 exhibited a half-life of about 6-9 days in plasma and CSF of both Tg and non-Tg mice, with a prolonged brain retention compared to plasma, and with the half-life more prolonged in brains of Tg mice than non-Tg (T1/2 was 18 days and 9.8 days Tg and non-Tg mice, respectively). The rec158 half-life was 2.7-fold longer in brain compared to plasma. Hence, a longer and target-dependent half-life of rec158 and lecanemab in brains of Tg mice was suggested. A single IV dose resulted in the dose-proportional increased of the

mean C5min and AUC0-384h in the serum from 10 to 100 mg/kg in male and female Sprague Dawley rats with half-life approximately of 9 to 12 days. All together the results suggest an expected Aβ-driven exposure, retention and elimination from the brain. Plasma half-life is comprised in the large range of known values for IgGs. No gender effect was identified.

Three PK studies were performed with lecanemab in male cynomolgus monkeys (SC, IV) Lecanemab (50 mg/kg) administered subcutaneously in study resulted in mean Cmax at 472 µg/mL, mean Tmax of 72h, mean AUC0-840h of 194,843 µg.h/mL and mean t1/2 was 10.5 to 13.0 days in the dose range.

2.5.3.3. Repeat-dose studies with lecanemab

Two TK studies were performed after repeated IV dosing of lecanemab in the cynomolgus monkey, once a week. At NOAEL (50 mg/kg), mean AUC(0-384h) for males and females were 93,000/228,500 µg·h/mL, and mean C5min were 1290 /2305 µg/mL for males and females on Day 1 / 29 (4-week intermittent IV dose toxicity study with 5-Week recovery period). The mean C5min, AUC0-168h, and AUC0-840h values increased dose-proportionally on Days 1 and/or 29 with no significant gender differences. Only investigated for the 50 mg/kg group, the serum concentration of lecanemab decreased slowly from Day 29, up to the end of recovery period on Day 64 (840h after dosing, corresponding to recovery), and the mean half-lives in were determined at the 13.3-19.6 days. Lecanemab accumulated a less than 2-fold between the first and fifth dose at 5, 15, and 50 mg/kg, but a more than 2-fold increase was observed in AUC0-168h a Day 29 at 5, 15, and 50 mg/kg.

In the 39-week intermittent intravenous dose toxicity study with 13-week recovery period, NOAEL (be 100 mg/kg, once a week) corresponded to mean AUC(0-384h) for males and females of 518,500 µg·h/mL, and mean C3h5min for males and females on Day 274 at 4455µg/mL. The mean AUC(0-168h) values increased dose-proportionally on Days 01, 92, and 274 with no apparent gender differences, however repeated administration led to significant accumulation of lecanemab as AUC(0-168h) increased on Day 92 versus Day 01 from 3.6-6.4-fold with increased dose level. It should be noted there were no differences between Day 274 versus Day 92 suggesting some saturation. After Day 274, the serum concentration at 100 mg/kg decreased slowly during the recovery period, and AUC on Day 365 up to 2% of the C3h5min value on Day 274. The mean half-lives in males and females were 419 and 410h, respectively, based on measurement in the recovery group.

The serum half-life of lecanemab was approximately 13-17 days in monkeys in the 4-/39-week repeat-dose toxicity studies in monkeys (2-12 days in rats and mice) that is comprised in the large range of known values for IgGs and in line with human T1/2 of lecanemab. In clinical trial BAN2401-A001-S101, it was found that the half-life in patients with Alzheimer's disease was ~6.8 days. Biacore studies showed lecanemab had a relatively high affinity with hFcRn at pH 6, but low interaction was observed between the hFcRn and lecanemab, which may partially account for the shortest plasma half-life of lecanemab in non-clinical species and humans compared to other IgGs.

2.5.3.4. Distribution

After a single IV, lecanemab exhibited a volume of distribution (65.1 mL/kg) justifying exhaustive distribution studies are not mandatory according to ICHS6 guideline.

While bioanalytical methods and studies were not conducted under GLP condition, it has been concluded no preferential partitioning in 3 types of blood from normal, elder and Alzheimer donors, and no plasma protein binding by comparison with lecanemab concentration from serum clinical sample, in line with usual consensus that the role of plasma protein binding in therapeutic antibody PK is usually

considered limited. Then binding to individual proteins (immunoglobulin, serum albumin, α1-acid glycoprotein, bilirubin….) was not deemed necessary.

Higher concentrations of ^{125}I-rec158 were found after IV in the brain, heart, lungs, kidney, liver, spleen stomach, thyroid and muscles of the non-Tg (aged 10 months) compared to the Tg2576 mice at Day 14 post administration, and with similar temporal profile of ^{125I}-rec158 for both these organs and plasma, excepted longitudinal decay-concentration profile showed kidney and bladder were exposed at before the other organs in both Tg2576 and non-Tg mice and at higher level. However, SPECT imagery also revealed high concentration of radioactivity in the liver. Given mAbs are not expected to be subjected to phase I/II metabolism enzymes, several mechanisms are reported in literature to be involved in the elimination of antibodies, and proteolysis in the liver and in the reticuloendothelial systems located in the liver is considered as common elimination pathway of antibodies. Then high concentration of radioactivity observed in the liver could represent antibody catabolised through proteolysis to small peptides and amino acids.

Comparison of the brain retention and plasma parameters of antibodies for studies in Tg-APPArcSwe mice versus Tg2576 mice, needs to consider the two used transgenic Tg mice strains exhibited differential expression levels of the pharmacologic target in the brain (Tg-APPArcSwe mice> Tg2576 mice). Then it may be supported Aβ protofibrils-driven brain retention of lecanemab would be more prolonged in Tg-APPArcSwe mice. Higher radioactive concentrations in several tissues of non-Tg mice (including brain) compared with Tg2576 mice was related to higher systemic exposure observed in the non-Tg mice. Histological data showed that Aβ levels in the vessel wall may be responsible for impaired cerebral blood flow in the Tg2576 mouse model in Kara et al. 2012 (*Kara F, E.S. van Dongen, R. Schliebs, M.A. van Buchem, H.J.M. de Groot, A. Ali. Monitoring blood flow alterations in the Tg2576 mouse model of Alzheimer's disease by in vivo magnetic resonance angiography at 17.6 T. NeuroImage, 2012, Volume 60, Issue 2, 2: 958-966*.). An exploratory pharmacology study from the package submission supported also regional blood flow significantly increased in the cortex of 19-month-old Tg2576 mice after 12 weeks of treatment of mAb158 supporting the evidence of altered brain perfusion in Tg mice. It is also well known that in AD patients, as in AD animal models, the deposition of amyloid β peptide in the cerebral vessel walls is known as cerebral amyloid angiopathy and is frequently observed, leading to blood flow abnormalities; changes in vascular structure were imaged non-invasively by magnetic resonance angiography in this mice model, and quantitative analysis revealed also severe blood flow defects in large and medium sized arteries. Normalisation of radioactive concentration in brain areas by corresponding plasma concentration (µg/mL) reflected better the brain tissues concentration of antibody. The normalised ratios in cortex and midbrain were higher in Tg2576 mice than non-Tg mice, supporting a Aβ protofibrils-driven brain retention of lecanemab. It should be noted some of the brain distribution and pharmacokinetic parameters were also studied from non-transgenic versus transgenic mice of different ages. Differences in systemic exposure occurred between the 10-month-old non-Tg mice and 23-month-old Tg2576 mice, the Cmax and AUC values of a labelled murine antibody being the lowest in Tg mice. Given drug elimination from systemic circulation is independent of absorption processes, and half-life from the elimination phase was similar, and the distribution volume is unaffected with age, it is considered that the tissue distribution of the antibody had not been impacted. When reasoning in term of normalised brain concentration value by the corresponding plasma concentration, studies supported higher brain distribution of the antibody in Tg mice than in non-Tg mice. Neither pharmacokinetics of lecanemab in pregnant animals nor transfer to maternal milk and progenitor was investigated. As a consequence, SmPC 4.6 Fertility, pregnancy and lactation section was required to highlight putative risks.

2.5.3.5. Metabolism and excretion

ICH S6 guideline states classical biotransformation studies have not to be conducted with therapeutic proteins. Lecanemab is a monoclonal antibody and is expected to break down to peptides and amino acids. mAbs are usually not expected to cause, or be susceptible to, hepatic Phase I/II metabolism. Excretion studies have not been performed for lecanemab. It is likely that lecanemab is eliminated as peptides or amino acids after catabolism as known for immunoglobulins and other therapeutic antibodies. Very high early concentrations of radioactivity in bladder and similar longitudinal uptake in kidney and bladder, in both Tg2576 and non-Tg mice after treatment with the radiolabelled surrogate ^{125}I-rec158, may support contribution of renal clearance. No renal excretion is expected in humans for lecanemab as the molecular weight is higher than the cut-off glomerular filtration.

2.5.3.6. Anti-drug antibodies (ADA)

Anti-lecanemab antibodies were generally at BLQ level in intravenous or subcutaneous studies in monkeys, including the 4/39-week intravenous general toxicology studies until the end of the recovery period, and the 4-week subcutaneous repeated-dose local tolerance. When anti-lecanemab antibodies were detected, they did not have significantly impacted serum AUC or Cmax of lecanemab in monkeys. However high immunogenicity was observed in Tg2576 mice following treatment by lecanemab and its human IgG control in all animals, then having limited extensive toxicology investigation in mice.

2.5.3.7. Pharmacokinetic drug interactions

Studies of pharmacokinetic drug interactions with lecanemab have not been conducted. Lecanemab is a humanised mAb where the primary elimination pathway is clearance by the reticuloendothelial system. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in clearance of lecanemab. Thus, the potential risk of interaction between lecanemab and other drugs is considered to be low.

2.5.4. Toxicology

2.5.4.1. Toxicological species

The relevance for the species selection for the proposed toxicology programme, is justified by the followings:

(i) Extensive safety assessments were conducted in the aged Tg mouse (Tg2576 and Tg APPArcSwe) using the surrogate murine monoclonal antibody for lecanemab to evaluate on-target toxicity of lecanemab. The particularity of the toxicological programme is on-target toxicity evaluation of cerebral microhaemorrhage potential can be conducted only as part of the non-GLP repeated-dose pharmacology studies in transgenic mice (Tg2576 and Tg-APPArcSwe) using the murine monoclonal antibody surrogate.

(ii) Standard non-clinical species used for toxicology studies do not have Aβ plaques, or significant levels of Aβ protofibrils. Due to low expression of amyloid precursor protein and subsequent low basal level of Aβ in healthy rats and cynomolgus monkeys, toxicology features from studies in these normal animals should be considered to document off-target toxicities. The off-target toxicity programme relied on intravenous toxicity studies, i.e., single-dose in rats (GLP) and monkeys (non-GLP), and 4- and 39-week repeated-dose

intravenous GLP toxicity studies in monkeys. Subcutaneous local tolerance (GLP) study was also performed in monkeys.

(iii) Cynomolgus monkey IgG1 has a similar sequence to human IgG1 and cynomolgus monkeys were considered generally predictive of the pharmacokinetics of such antibodies in humans.

(iv) *In vitro* GLP tissue cross-reactivity of lecanemab was evaluated using a full panel of fresh-frozen rat, cynomolgus monkey, and human tissues. Based on the results of tissue cross reactivity studies, which were available at the time of animal species selection, no reactivity of lecanemab was detected in normal human or cynomolgus monkey brain tissue

Batches used in the whole GLP toxicology studies had similar purity (>99%).

2.5.4.2. Single dose toxicity

There were no deaths and no treatment-related changes in clinical signs, body weights, food consumption, haematology, blood chemistry, urinalysis, ophthalmologic examination, organ weights or macroscopic and microscopic pathology at any dose in both a GLP study where Lecanemab was administered as a single intravenous bolus injection to male and female Sprague Dawley rats at doses up to maximal dose 100 mg/kg and a non-GLP single intravenous dose range toxicity study of lecanemab in male monkeys maximal dose tested 50 mg/kg. These doses provided large exposure relative the human clinical exposure at 10 mg/kg, but given the clinical regimen, repeat-dose toxicity studies are the most suitable to document the toxicity profile of lecanemab.

2.5.4.3. Repeat dose toxicity

The use of a single specie cynomolgus monkeys for off-target repeat-dose toxicity studies is supported by tissue cross-reactivity studies. When lecanemab was applied to a larger panel of tissue from normal rat and cynomolgus monkey tissues, the results showed no lecanemab-specific staining in rat tissues, and the cytoplasmic staining was observed. Such staining within the cytoplasm is usually not considered toxicologically relevant but related to permeabilisation artefact as mAbs would not be able to reach cytoplasmic compartment in vivo. In addition the applicant provided further discussion for cross-reactivity of lecanemab with cryosections of normal human tissues, giving insight that some forms of amyloid, other amyloid-related peptides or amyloid-mediated complex may account for the intracellular staining in neurons, glial cells, pancreatic islet cells and possibly in epithelium (mainly kidney, whole gastrointestinal tract system, salivary gland acini and ducts, liver, pancreas, pituitary adenohypophysis endocrine cells, reproductive system and placenta trophoblasts and thyroid) and mononuclear cells.

The top dose in monkeys was the maximum feasible concentration of 50 mg/kg/week allowed with the dose formulation at a concentration of 10 mg/mL and the dose volume limits with a single intravenous bolus injection. No death occurred in both off-target toxicities conducted in cynomolgus monkeys with lecanemab administered through the saphenous vein once a week for 4 and 39 weeks. In a 4-week non-pivotal intravenous toxicity study in monkeys (0, 5, 15, and 50 mg/kg), only increases in absolute weight and the size and number of germinal centres in the spleen were observed as adaptive response, and there was no toxicologic change at any examinations including the safety pharmacologic tests (tests for CNS, respiratory function, or cardiovascular system).

In line with splenic changes observed in the 4-week study, treatment-related changes were limited to the spleen in groups receiving 15 to 100 mg/kg in the 39-week study, *i.e.* increase in splenic weight with highest relative weight increase (approximately up to 40%) at 100 mg/kg. Histopathologically,

minimal increase in germinal centres occurred in controls and all treatment groups, with higher incidence for mild increase in germinal centres in the 100 mg/kg group. Findings reversed for the 39-week and 4-week repeat dose studies in the recovery periods of 5 weeks and 13 weeks, respectively. From the pivotal 39-week repeated-dose toxicity study in cynomolgus monkeys, the average Cmax and AUC (on Day 274) at the NOAEL (100 mg/kg/week) was 4,455 µg/mL and 518,500 µg·h/mL, respectively. Then animals were sufficiently exposed, during the whole dosing period, relative to the human dose. Once weekly dosing resulted in safety margin levels of 27/14-fold (AUC/Cmax) for off-target toxicity profile in monkeys.

Given the lack of any other lecanemab-related findings, reversibility, low amplitude changes, and as germinal centre expansion has been described as adaptive response to immunogenic foreign proteins with B cells proliferating in response to an antigen, the human relevance of these spleen findings may be limited in term of immunotoxicity. *In silico* approaches suggest that the antibody variable region sequences were considered to be associated with a significant risk of immunogenicity given several sequences contained a total of 7 promiscuous high affinity and 5 promiscuous moderate affinity MHC class II binding peptides. However experimental *ex vivo* EpiScreen™ technology were conducted to assess overall T-cell responses through [^{3}H] thymidine uptake and interleukin-2 production. An *ex vivo* time course T-cell proliferation assay performed with peripheral blood mononuclear cells from 25 healthy donors with a broad HLA-diversity PBMCs showed 3 donors/25 displayed positive T-cell responses for proliferation based on [^{3}H] thymidine uptake. Combined interleukin-2 secretion assay confirmed PBMCs from 2 donors displayed positive T-cell responses for proliferation. Positive responses in PBMCs from 2 or 3 donors corresponded to 8 or 12 %. In general, protein therapeutic agents that induce greater than 10% positive responses in both combined EpiScreen™ assays are associated with an increased risk of immunogenicity in the clinic. Given the threshold is exceed for only one test and not both, lecanemab-induced low frequency of positive responses supports a low potential for human risk of immunogenicity/immunotoxicity. Given the age of AD patients, juvenile toxicity studies are not mandatory.

- Microhaemorrhage, inflammatory changes, or microglial activation in the brain have been reported throughout literature for anti-Aβ antibodies, contributing to exacerbated cerebral amyloid angiopathy-related microhaemorrhage in various Tg models including Tg2576 mice. Tg2576 mice are known to exhibit significant increases in Aβ-plaque deposition from9 months of age. Older Tg2576 mice have a widespread parenchymal Aβ deposition as well as Aβ deposition in cerebral vasculature (*i.e.,* cerebral amyloid angiopathy) as seen in AD patients. Tg-APPArcSwe mice are rich in amyloid deposits with substantial amount of intracellular soluble Aβ aggregates, exhibit early parenchymal and vascular amyloidosis, and generate of senile plaques. Then these Tg mice are appropriate models for investigating potential mechanism-based toxicologic effects of anti-protofibril monoclonal antibody. Given aggressive behaviour of males of Tg2576 mice and other amyloid-based mouse models of Alzheimer's disease have been described in literature, the applicant used primarily female mice to assess the potential cerebral microhaemorrhage of lecanemab. No histopathological changes, microhaemorrhage or hemosiderin deposit were detected in any group in the brain of the young 4-month-old Tg2576 mice treated once a week for 4 months with mAb158 despite up to 50% decrease of protofibril/oligomer contents in brain mAb158. No mAb158-related sign of microhaemorrhage, inflammatory changes, or microglial activation were detected in the brain of older 53-week-old female Tg2576 mice following administration of mAb158 up to 50 mg/kg for 18 weeks (providing an equivalent systemic exposure (Cmax = 585 µg/mL and AUC(0-168h) = 67,450 µg·h/mL; multiple of exposure ≤ 2-fold) to human clinical exposure) despite concomitant 80% decrease of brain Aβ. In 12.5-month-old Tg2576 mice, mAb158 reduced brain Aβ protofibril level by approximately 3-fold after treatment with 12-24 mg/kg/week mAb158 for 18 weeks without difference in incidence of microhaemorrhage/hemosiderin deposits between mice

treated with mAb158 or PBS. When the 18–24-month-old Tg-APPArcSwe mice were treated for 3 months up to 12 mg/kg, no differences in microbleeding between mice treated with mAb158 and placebo were observed while a statistically significant 52% reduction in Aβ protofibril levels was observed in the mAb158-treated animals compared to placebo-treated mice. To conclude there are no evidence mAb158 (or lecanemab) would have the potential to elicit microhaemorrhages. It should be noted that the presence of ADAs had a profound effect on exposure mAb158, decreasing mAb158 levels by approximately 100-fold and AUC(0-168h) exposure by 10- to 20-fold in the 50-mg/kg/week group in Tg mice, thus limiting investigation of toxicity at higher exposure.

2.5.4.4. Genotoxicity and Carcinogenicity

Lecanemab is a large protein molecule that is not expected to cross the nuclear or mitochondrial membranes and interact directly with DNA or other chromosomal materials. Studies evaluating genotoxicity of biotechnology products, are not mandatory in accordance with ICH S6 guideline, which states proteins as Lecanemab are unlikely of genotoxic potential.

As permitted by ICHS1/S6 guidelines, a weight-of-evidence assessment of carcinogenicity risk was conducted, suggesting lecanemab has a low carcinogenic potential based on experimental and literature data taking into account the lack of genotoxic potential of mAb, lack of histopathology features such as hyperplasia, hypertrophy, altered foci or immunosuppression the pivotal 39-week repeat-dose toxicity studies, inverse association between cancer and AD from human data, no reported evidences for an incidence of tumours in APP knock-out mice or transgenic mice engineered to over-express human APP.

2.5.4.5. Reproductive and developmental toxicity

In the 39-week toxicity study in cynomolgus monkeys with doses up to 100 mg/kg/week, oestrous cycle, organ weights, and histopathologic evaluation demonstrated that male or female reproductive organs are not target organs of toxicity for lecanemab. This is in accordance with the ICH guideline S6(R1) hence, the assessment of fertility is considered adequate. No reproductive and developmental toxicity study was conducted with lecanemab. This was justified by the applicant according to a weight of evidence approach considering notably that the age of the intended patient population (50 years of age and older). In addition, it was pointed out that standard preclinical models used for the conduct of reproductive and developmental studies are not relevant since the soluble aggregates of Aβ targeted by lecanemab are not detectable in these species. Moreover, a review of the literature was performed to understand any role of APP and presumably its cleaved Aβ isoforms on fertility, embryofetal development, or post-partum survival. To summarise, findings suggestive of impaired postnatal neuromuscular and neuronal functions were reported in mice with disrupted βAPP or APP ko mice, but it is not known if these effects could be induced with Aβ or APP inhibition solely restricted to the period of gestation.

2.5.4.6. Tolerance

Based on single and repeat dose intravenous toxicity studies in rats and cynomolgus monkeys, and 4- and 39-week intermittent intravenous repeated-dose toxicity study in cynomolgus monkeys, there were no findings suggesting local irritation at the injection site at any dose level.

In a further repeated-dose local tolerance study in cynomolgus monkeys was performed with subcutaneous dosing of lecanemab for 4 weeks (every day for 4 weeks) at a dose level ensuring

sufficient exposure (2.46- fold (or 11.48-fold when corrected for similar interval) the human exposure at the clinical dose), there were no test article-related changes in any of the gross pathology, histopathology or clinical pathology assessment as all changes were comparable to those observed in the control animals.

2.5.4.7. Other toxicity studies

2.5.4.7.1. Antigenicity

No ADAs to lecanemab were detected in the serum samples from i.v. repeat-dose toxicity and s.c. local irritation studies in cynomolgus monkeys. However, there is low predictivity in animals for antibody formation in humans.

2.5.4.7.2. Immunotoxicity

No stand-alone immunotoxicity study of lecanemab were conducted. Instead, potential immunotoxicity of lecanemab was evaluated in standard toxicity parameters as part of the 4- and 39-week i.v. repeat-dose toxicity studies in cynomolgus monkeys. Increasing trends in mean absolute and relative weights, size, and number of germinal centres in the spleen were observed in both studies; however, these changes were considered to be adaptive response to the i.v. injection of a foreign protein. Given the lack of any other lecanemab-related observations, the relevance of these spleen findings to humans is expected to be of limited significance. In EpiScreen™ assays, T-cell proliferation and interleukin-2 production using peripheral blood mononuclear cells from 25 healthy donors with broad HLA-diversity, lecanemab induced a low frequency of positive responses with a combined assay response rate reflective of a low predictive risk of clinical immunogenicity.

2.5.4.7.3. Dependence

Lecanemab is not chemically or pharmacologically similar to known drugs of abuse and will be administered by a healthcare provider. Lecanemab has a long half-life and signs and symptoms of withdrawal or rebound are not expected. No behavioural signs were noted with lecanemab from non-clinical studies or clinical data to indicate abuse potential. Hence, the applicant provided a satisfactorily justification for not conducting dependence studies.

2.5.4.7.4. Metabolites

No studies to determine lecanemab metabolites were conducted. Lecanemab is a monoclonal antibody and expected to be fully metabolised into small peptides and amino acids via catabolic pathways in the body. Therefore, the absence of studies to determine metabolites is accepted.

2.5.4.7.5. Studies on impurities

It is concluded that impurities' levels are sufficiently low compared to qualified toxicological limits, resulting in sufficient safety margins.

2.5.4.7.6. Other studies

The tissue cross-reactivity studies identified no potential in vivo risk of lecanemab.

2.5.5. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, an environmental risk assessment is not required for amino acids, peptides or proteins because they are unlikely to result in significant risk to the environment. Therefore, lecanemab is considered to be no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

2.5.6. Discussion on non-clinical aspects

The dogma in Alzheimer's disease (AD) is the pathophysiology of the disease, while not fully understood, is associated to accumulation of Aβ-containing plaques and tau-containing neurofibrillary tangles in the brain and given initiation of cerebral amyloid deposition occurs over a decade before clinical symptoms of AD, the "amyloid hypothesis" is the rational for the use of lecanemab in AD humans. Aβ peptides resulting from cleavage of the amyloid precursor protein (APP), gives rise to misfolding and self-aggregation, including monomeric Aβ, soluble Aβ assemblies (low-molecular weight oligomers and higher-molecular weight protofibrils) and insoluble fibrils. Increasing evidence has suggested in 2000s that the levels of soluble Aβ oligomers and protofibrils may better correlate with disease severity than insoluble plaque load or monomeric Aβ levels, as soluble Aβ oligomers and protofibrils have been implicated in mediating neurotoxicity, altering synaptic function, and inhibiting hippocampal long-term potentiation. A comprehensive package of *in vitro* and *in vivo* studies was designed to characterise the pharmacological properties of lecanemab, a humanised immunoglobulin G (IgG)1 monoclonal antibody (mAb) with respect to its mechanism of action, PK, pharmacodynamics, and toxicological profile. Studies were performed using either lecanemab, or the surrogate murine mAb (mAb158), and an allotype-variant murine homologous recombinant protein of mAb158 (rec158).

The nonclinical safety testing strategy for lecanemab relies mainly on the relevant ICH S6(R1) 'Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals'. Neither genotoxicity studies nor reproductive and developmental toxicity studies were conducted, because these studies are not usually considered fully relevant for biotechnology products or may be questionable for human translation with regard to the ICHS6 guideline. A weight-of-evidence assessment of carcinogenicity risk was conducted considering this possibility afforded by ICH S6 and S1 guidelines instead of conducting 2-years carcinogenicity study in rodents and 6-month Tg Ras study to support long-term human use of lecanemab. The whole approach is supported.

In vitro pharmacology studies mainly investigated (i) the binding of lecanemab and mAb158 to Aβ protofibrils, other Aβ species, and Aβ fragments; (ii) the effect of lecanemab and mAb158 on β-sheet formation of Aβ, binding to hippocampal neurons and on Aβ protofibril-induced neuronal cell toxicity; (iii) effect of lecanemab on Aβ oligomer-induced long-term potentiation (LTP) impairment in hippocampal slices; (iii) binding of lecanemab and mAb158 to FcγRI, FcγRII, and FcγRIII; (iv) effect of lecanemab on Aβ protofibril uptake in microglial cells; (v) off-target potential and immunogenicity risk of lecanemab.

There is a body of evidence lecanemab showed the high affinity for the soluble Aβ protofibrils. Binding mode includes the three first amino terminal amino acids of amyloid and the Fab moiety. Lecanemab to binds FcγRI and FcγRIII, and studies supported ADCP/FC-mediated Aβ uptake by microglia from cultured Alzheimer's disease microglia, and Aβ clearance through enhanced Fc-related phagocytosis after opsonisation of protofibrils by lecanemab. Lecanemab was protective against Aβ oligomer-induced long-term potentiation (LTP) impairment in hippocampal slices and displayed a neuroprotective potential against Aβ 1-42 protofibrils and oligomer-induced neuronal toxicity in primary cortical chicken neurons, neuroblastoma SHSY-5Y cells or rat primary medial septum neurons. Taken together, these

findings suggest lecanemab is able to reverse the deficit in LTP produced by Aβ, as a hallmark of synaptic activity. *In vitro* primary pharmacology data are considered sufficient and comparative binding profile with other amyloid-targeting antibodies had been attempted showing higher and preferential avidity for protofibrils for lecanemab.

In vivo pharmacology studies were conducted in amyloid precursor protein (APP) transgenic (Tg) mice (Tg-APPArcSwe andTg2576) and APP knock-in mice (APPNL-G-F) with mAb158 or rec158, mainly to investigate short sand long-term effects on Aβ protofibril levels (and Aβ monomer levels, plaques) as well as functional imaging of cerebral blood flow and behaviour. Based on literature about phenotype characterisation, the age at time of treatment for the strains used in a majority of the pharmacology studies would be compatible with ongoing physiopathology development or established significant brain amyloid accumulation and plaque, and behavioural deficits, with the limitation that studies employing youngest animals may not have developed enough amyloidosis during the treatment period to affect baseline learning and memory.

Reduction in brain amyloid β protofibrils (soluble, insoluble fraction) was demonstrated in most of studies using Tg2576 mice, APPArcSwe mice and/or AppNL-G-F knock-in mice with mAb158 at clinically achievable concentration, as well as decreased in CSF in several studies when measured. Reduction in plaque was observed in a more fragmented manner observed in some studies only. To conclude on a putative effect on differential reduction of Aβ 1-40 and Aβ 1-42 species is uncertain. It is furthermore noted that only female Tg2576 mice are used in the *in vivo* pharmacology studies, which has not been justified by the applicant. It would seem there are some sex differences in humans, implying higher exposure in women, which could warrant a discussion on the selection of animals by the applicant, and the potential influence of PK parameters on the efficacy in males. No data has been provided comparing the PK profile in male and female mice. PK data in rats indicates no sex differences. It is also noted that both male and female Tg-APPArcSwe mice are used in the in vivo PD studies, which do not seem to indicate a significant difference in pharmacological response between males and females. The issue is therefore not further pursued.

mAB158 treatment did not enhance contextual fear memory while decreasing significantly 5-fold the brain Aβ protofibril content in Tg mice. While fear conditioning has been traditionally used to address cognitive deficit in 10 months-Tg2576 mice other behavioural tests could have been employed as having evident deficit at this age in Tg2576 mice (*Webster Scott J., Adam D. Bachstetter, Peter T. Nelson, Frederick A. Schmitt, and Linda J. Van Eldik. Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models. Front Genet. 2014; 5: 88*.), including spatial memory tests (Morris water maze, radial arm water maze), learning tasks (passive avoidance), alternation tasks (Y-Maze/T-Maze alternation), recognition memory tasks (Novel Object Recognition). Given the lack of cognitive improvement in the fear conditioning assay and no data from other relevant behavioural (spatial learning and memory abilities) tests, there is no proof supportive for cognitive improvement. Evidence for improvement of cognitive deficit was not investigated by the applicant in the two other AD models while spatial learning impairment in the Morris water maze (4-8 months) and in an Intellicage-based Passive Avoidance test (16 months) have been observed in Tg-APPArcSwe mice (*Lord A, Englund H, Söderberg L, Tucker S, Clausen F, Hillered L, Gordon M, Morgan D, Lannfelt L, Pettersson FE, Nilsson LN. Amyloid-beta protofibril levels correlate with spatial learning in Arctic Alzheimer's disease transgenic mice. FEBS J. 2009 Feb;276(4):995-1006; Codita Alina, Astrid Gumucio, Lars Lannfelt, Pär Gellerfors, Bengt Winblad, Abdul H. Mohammed, Lars N.G. Nilsson. Impaired behavior of female tg-ArcSwe APP mice in the IntelliCage: A longitudinal study. Behavioural Brain Research, Volume 215, Issue 1, 20 December 2010, Pages 83-94.),* and memory impairment as measured by the Y maze starting at 6 months in the AppNL-GF Knock-in mice (*Saito T, Matsuba Y, Mihira N, Takano J, Nilsson P, Itohara S, Iwata N, Saido TC. Single App knock-in mouse models of Alzheimer's disease. Nat Neurosci. 2014 May;17(5):661-3.).* On the other hand,

whether the proof of concept for correction of cognitive deficit is mandatory for lecanemab may be debatable as behavioral rescue has not always observed in AD models while targeting amyloid forms/aggregates (*Chen G, Chen KS, Kobayashi D, et al. Active beta-amyloid immunization restores spatial learning in PDAPP mice displaying very low levels of beta-amyloid. J Neurosci. 2007;27(10):2654-2662*), and there is a consensus to consider partial predictivity for human translation of behavioural studies from AD models. The lack of a convincing correlating biological response in the cognitive functioning assays that were performed, as well as the lack of further *in vivo* assays to substantiate the pharmacological action of lecanemab in AD, does not support the current claim of a beneficial effect in AD from a non-clinical point of view. On the other hand, publication by Drummond E and Wisniewski T. (*Alzheimer's disease: experimental models and reality. Acta Neuropathol. 2017 Feb;133(2):155-175*) reported successful non-clinical investigations that resulted in failed clinical trials for Aβ antibody therapeutic agents.

Deficits in regional perfusion in the tempo-parietal regions of the brain are associated with mild cognitive-impairment, dementia, and Alzheimer's disease in humans. A 12 weeks-mAb158 (50 mg/kg/week) treatment from the 19 months-old Tg2576 resulted in significant reduction in plaque load in treated mice when compared to untreated mice in the hippocampus (7-18%) and cortex (9-25%) with a possible increase in blood flow in these regions and improved neuronal viability, but there was no benefit on glucose utilisation. However, these results should be considered exploratory as amyloid β levels in the CSF and soluble brain homogenate were not significantly different from the vehicle group, and the apparent significant difference in mean amyloid Beta plasma level should be considered not relevant due to the 62 % CV in the vehicle group. In addition there are limitations given no wild type control mice were included, the mortality/attrition rate was 50%, and data from the FDG study may be unconclusive as Tg2576 are hypermetabolic then glucose metabolism investigation may have been impaired (*Luo Feng, Nathan R Rustay, Ulrich Ebert, Vincent P Hradil, Todd B Cole, Daniel A Llano, Sarah R Mudd, Yumin Zhang, Gerard B Fox, Mark Day. Characterization of 7- and 19-month-old Tg2576 mice using multimodal in vivo imaging: limitations as a translatable model of Alzheimer's disease. Neurobiology of Aging 2012, 33: 933-944*). Then data from this study should be considered unconclusive.

To conclude on the lack of *in vivo* cognition/functional improvement in the pharmacology programme, (i) the review of literature had highlighted other behavioural tests could have been performed but there were limitation of behavioural endpoints in transgenic AD models to translate animal proof-of-concept to humans; (ii) literature review also reported successful non-clinical investigations that have result in failed clinical trials for Aβ antibody therapeutic, then it seems sufficiently justified that both negative and positive results in *in vivo* behavioural studies would not be of high predictive value for clinical efficacy; (iii) regarding the mode of action, *in vivo* non clinical studies support the decrease of protofibrils brain level occurred at achievable clinically concentration. Then it is concluded there is limited ability of animal studies in the models of AD to provide translatable outcomes on functional/behavioural outcomes in humans with lecanemab apart demonstration of Amyloid β targeting and protofibril/plaque clearance, which was observed with mAb158.As a consequence any evidence of functional efficacy and use benefit of lecanemab should be established in clinical trials, as no reliable non-clinical evidence is available to support the claim, and could not be obtained. This consideration is part of the B/R assessment.

Off-targets for thrombospondin-1, fibrinogen chains, proenkephalin, or amyloid A4 may be considered reasonably unlikely : human plasma thrombospondin-1 concentration of was estimated 1000-fold lower than lecanemab; no safety concern as fibrinogen-related clotting disorders were observed from clinical studies and non-clinical toxicology studies; no pain, renal or cardiac dysfunction have been associated to proenkephalin A, which its receptors are widely distributed and involved in these tissue and function; targeting of amyloid A4 protein in pathological conditions is favourable as A4 protein is found

in cerebrovascular amyloid deposits, as well as in the core of the neuritic plaques in the brain tissue of patients afflicted with Alzheimer's disease.

Although CDC and ADCC assays have not been performed, C1q interaction, binding to FcγR IIIa, and putative related risks for increased effector CDC and ADCC functions were derisked through appropriate Applicant' discussion and the lack of findings at non clinical and clinical level are sufficient to support: the mechanism of action of lecanemab that is binding of the soluble Aβ species rather than potential targeting of membrane antigen, which did not favour recruitment of Natural Killer cells or macrophages to elicit cell-mediated cytotoxicity, or IgG hexamerisation for activation of the complement pathway; lack of T cells activation in Episcreen™ assay, there were no anaphylatoxin/complement activation products-related pro-inflammatory, sepsis or immune effects, complement-mediated RBC lysis with release of RBC constituents, leucopenia, or and/or cytokine release in animals and humans). However, whether analytical control strategies when releasing batches was appropriate to avoid unwanted ADCC/CDC potential is out of the scope of the non-clinical assessment and should be carefully addressed at Quality level to avoid release of further batches with unwanted enhanced ADCC/CDC potency compared to already released clinical batches.

Relevant pharmacodynamic drug interaction studies with other substances likely to be taken concomitantly were not addressed in animals, this is agreed.

The PK profiles of lecanemab were assessed in rats and cynomolgus monkeys after a single- or repeated-dose administration. The PK profile of lecanemab was also evaluated in cynomolgus monkeys after a single subcutaneous or intravenous administration. In addition, the PK profile of mAb158 was assessed in Tg2576 mice after a single-dose administration. The PK profiles of lecanemab and rec158 were also explored in Tg-APPArcSwe mice after a single-dose administration. Cmax and AUC values were measured in the plasma and CSF, and anti-lecanemab antibodies were searched. Lecanemab and surrogates had on the whole usual parameters as other therapeutic antibodies. Plasma protein binding, blood partitioning studies and literature on therapeutic antibodies suggested low plasma protein binding of lecanemab, and there is low evidence for significant difference in drug exposure in humans between healthy, aged and pathological conditions. Normalisation of radioactive concentration in brain areas by corresponding plasma concentration (µg/mL) reflected the brain tissues concentration of antibody, and the normalised ratios in cortex and midbrain were shown higher in Tg2576 mice than non-Tg mice, supporting a Aβ protofibrils-driven brain retention of lecanemab. No formal metabolism, excretion or DDI studies were performed as often for biotechnology-products developed under ICHS6, as the fate of proteins after administration is well known, and mAb are not expected to cause, or be susceptible to, hepatic Phase I/II metabolism, and PK drug interactions with concomitantly administered medications. Despite some distribution and single-dose PK studies had been conducted as exploratory studies and with non-validated bioanalytical methods, the ADME programme is considered sufficient for detection of lecanemab/surrogates for PK profiling and toxicokinetics, as well as ADAs detection. These studies resulted in demonstration of brain penetration and plasma half-life comprised within the range of half-lives published for humanised monoclonal antibodies. ADA presence had been concluded to not having significantly impacted serum AUC or Cmax of lecanemab in several toxicological studies.

The pivotal toxicology studies were conducted in accordance with GLP regulations by laboratories in countries that adhere to the Organisation for Economic Cooperation and Development (OECD) Mutual Acceptance of Data (MAD) system. The toxicity of lecanemab was evaluated in single-dose intravenous (the intended clinical route of administration) toxicity studies. Soluble amyloid level is low in non-pathologic animals, then normal rats or monkeys may not be fully relevant species for extrapolating safety findings to AD humans since normal young animals used in toxicology studies do not have Aβ plaques or express Aβ protofibrils, and cynomolgus monkeys and rats are considered relevant for the off-target toxicity in humans. However, given that cynomolgus monkey IgG1 has a similar sequence to

human IgG1, monkeys are generally predictive of the pharmacokinetics of such antibodies in humans, and they may also be considered as a relevant species for assessing potential off-target toxicity of lecanemab. Then 4-(including safety pharmacology parameters) and pivotal 39-week repeated-dose iv toxicity studies were done. A local irritation study completed the panel of studies in monkeys by SC route. On target toxicity in humans can be documented from studies in knock-in mice, overexpressing human Aβ. As well, unwanted micro-haemorrhage potential in the brain was investigated during some pharmacology studies in Tg mice (Tg2576 and Tg-APPArcSwe) using the surrogate murine antibody mAb158, with concurrent histopathology of organs/tissues. *In vitro* tissue cross-reactivity of lecanemab was evaluated using a full panel of fresh-frozen rat, monkey, and human tissues. The whole safety approach is considered accepted.

Lecanemab was expected to react with extracellular amyloid β peptides at in the brain/cerebrum in humans, but in *vitro* tissue cross-reactivity assay showed intracellular staining in neurons, glial cells, pancreatic islet cells and possibly in epithelium (mainly kidney, whole gastrointestinal tract system, salivary gland acini and ducts, liver, pancreas, pituitary adeno-hypophysis endocrine cells, reproductive system and placenta trophoblasts and thyroid) and mononuclear cells in some organs/tissues. While such staining may account for cross-reactivity with other intracellular amyloid-related as discussed in the corresponding study report, cytoplasmic staining is usually considered not toxicologically relevant given monoclonal antibodies are not able to cross the non-permeabilised cell membrane (Hall W et al., 2008).

Treatment-related changes were limited to the spleen with increased splenic weight and incidence of germinal centres occurred in controls and all treatment groups. Given the lack of any other lecanemab-related finding, reversibility, low amplitude changes, safety margin levels and as germinal centre expansion is a known adaptive response to immunogenic foreign proteins with B cells proliferating in response to an antigen, the human toxicological relevance of these findings may be limited, and increased risk of immunogenicity/immunotoxicity had been derisked through combined EpiScreen™ assays. No histopathological changes, microhaemorrhage or hemosiderin deposit were detected in Tg mice weekly treated in long-term pharmacology studies in which statistically significant reduction in Aβ protofibril levels occurred. On the one hand there is no evidence that mAB158 has the potential to elicit microhaemorrhages in the condition of studies in mouse AD models; on the other hand, it should be noted that ADAs dramatically lowered antibody exposure, thus limiting investigation of toxicity with higher exposure multiple than 2-fold. Given this ADA-limiting exposure, one cannot formerly exclude occurrence of haemorrhage in lecanemab-treated humans based only on these studies, considering also report of ARIA-H (approximately 14%) and human haemorrhages (126/898 patients in the clinical Phase III trial).

No developmental or reproductive toxicity studies have been conducted. This was justified by the applicant according to a weight of evidence approach whose conclusions are generally supported, considering notably the age of most targeted patients and the limited relevance of standard preclinical models which do not express the targeted aggregate Aβ species. However, a small proportion of fertile patients may be treated with lecanemab since the proposed indication includes early Alzheimer's disease (EAD) patients. It is also noted that the incidence of agenesis of the corpus callosum was increased in mice with disrupted βAPP protein (*Müller U, Cristina N, Li Z-W, et al.,1994, Behavioural and anatomical deficits in mice homozygous for a modified β-amyloid precursor protein gene. Cell 79(5): 755–765*). This may represent a safety signal related to prenatal exposure to lecanemab since this brain structure is formed *in utero*, whereas there is some uncertainty regarding the relevance of impaired postnatal neuromuscular and neuronal functions reported in murine models with disrupted / KO βAPP for exposure to lecanemab during gestation. As a consequence, SmPC 4.6 has been amended to reflect potential exposure of the foetus and breastfed infant to lecanemab, as well as *ad hoc* measures to avoid exposure of foetuses and breastfed infants to lecanemab. Finally, SmPC 5.3

highlights that no studies in animals have been conducted to assess the effects of lecanemab on male or female fertility or developmental and reproductive function. No adverse effects on male or female reproductive organs were observed in a 39-week intravenous toxicity study in monkeys administered lecanemab weekly at doses up to 100 mg/kg (corresponding to plasma exposures 27-fold higher than in humans at the recommended dose). It is stated the relevance of these data to humans is limited since aggregate Aβ species are not present in healthy monkeys.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, lecanemab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The *in vitro* pharmacology programme is considered sufficient but there is limited ability of animal studies in the models of AD to demonstrate and to provide translatable outcomes on functional/behavioural outcomes in humans with lecanemab, apart demonstration of amyloid β targeting and protofibril/plaque clearance, with the surrogate antibody mAb158. Any evidence of functional efficacy and use benefit of lecanemab should, therefore, be traced back to clinical evidence. The safety had been adequately addressed from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The clinical development includes 8 ongoing or completed studies in 2203 lecanemab-treated subjects and 1300 placebo (PBO)-treated subjects with early Alzheimer's disease (EAD) (PBO [n=1142], lecanemab [n=2045]) and preclinical AD (PBO [n=158], lecanemab [n=158]).

Table 1. Summary of lecanemab studies

Study Number	Study Design/Population	Lecanemab Dose Regimen	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
BAN2401-A001-101 (Study 101) Total sites: 15	Double-blind, Randomized, Placebo-controlled, Combined Single Ascending Dose and Multiple Ascending Dose Study to Assess Safety, Tolerability, Immunogenicity, Pharmacodynamic Response, and Pharmacokinetics of Intravenous Infusions of lecanemab in Subjects With Mild to Moderate AD aged ≥50 years	SAD 0.1 mg/kg (SAD1) 0.3 mg/kg (SAD2) 1 mg/kg (SAD3) 3 mg/kg (SAD4) 10 mg/kg (SAD5) 15 mg/kg (SAD6) MAD 0.3 mg/kg (MAD1) 1 mg/kg (MAD2) 3 mg/kg (MAD3) 10 mg/kg (MAD4)	SAD Randomized/completed: 36/35 PBO Randomized/completed: 12/11 Sex: 7M/5F Race: 10W, 1B, 1A *APOE4* carrier: 5Y, 7N LEC0.1 Randomized/completed: 6/5 Sex: 2M/4F Race: 5W, 1B *APOE4* carrier: 2Y, 4N LEC0.3 Randomized/completed: 6/6 Sex: 4M/2F Race: 4W, 1B, 1A *APOE4* carrier: 4Y, 1N, 1UNK LEC1 Randomized/completed: 6/6 Sex: 4M/2F Race: 6W *APOE4* carrier: 2Y, 3N, 1UNK LEC3 Randomized/completed: 6/6 Sex: 3M/3F Race: 3W, 3B *APOE4* carrier: 3Y, 3N	SAD At predose, immediately at the end of the infusion, and 0.5, 1, 2, 4, 8, and 24 hours after the end of the infusion, and a single sample on Day 10, Day 21, Day 28, Day 90 (final visit for SAD6), Day 180 (final visit for SAD1 through SAD5), or at the Early Withdrawal Visit (if applicable). MAD1 to MAD3 Cohorts At predose and immediately at the end of the infusion for all 4 doses. Additional samples were collected at 30 minutes, 1, 2, 4, 8, and 24 hours after the end of the infusion Dose 1 and Dose 4, and a single sample at any time on Days 21, 49, 175, 264 (Final Visit), and Early Withdrawal (if applicable). MAD4 Cohort Blood was taken for lecanemab assays at predose for all 7 doses. Additional samples were collected immediately at the EOI, 30 minutes, 1, 2, 4, 8, and 24 hours after the end of the infusion at Dose 1 and Dose 7, and a single sample at any time on Days 98, 175 (Final Visit)/Early Withdrawal (if applicable).
Study Number	**Study Design/Population**	**Lecanemab Dose Regimen**	**Total No. of Subjects Randomized/Completed Sex, Race**	**PK Sampling Schedule**
			LEC10 Randomized/completed: 6/6 Sex: 4M/2F Race: 6W *APOE4* carrier: 4Y, 2N LEC15 Randomized/completed: 6/6 Sex: 1M/5F Race: 4W, 2B *APOE4* carrier: 3Y, 2N, 1UNK MAD Study Randomized/completed: 32/28 PBO Randomized/completed: 8/8 Sex: 6M/2F Race: 6W, 1B, 1O *APOE4* carrier: 4Y, 3N, 1UNK LEC0.3-M Randomized/completed: 6/5 Sex: 4M/2F Race: 4W, 1B, 1O *APOE4* carrier: 5Y, 1N, 0UNK LEC1-M Randomized/completed: 6/4 Sex: 1M/5F Race: 4W, 2B *APOE4* carrier: 5Y, 1N	

Study Number	Study Design/Population	Lecanemab Dose Regimen	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
			LEC3-M Randomized/completed: 6/5 Sex: 2M/4F Race: 5W, 1B *APOE4* carrier: 3Y, 3N	
			LEC10-BW Randomized/completed: 6/6 Sex: 4M/2F Race: 5W, 1B *APOE4* carrier: 2Y, 4N	
BAN2401-J081-104 (Study 104) Total sites: 7	Double-Blind, Randomized, Placebo-Controlled Study to Assess Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Pharmacodynamic Response of Repeated Intravenous Infusions of lecanemab in Subjects With MCI due to AD and Mild AD aged 50 to 90 years, inclusive	2.5 mg/kg (Cohort 1) 5 mg/kg (Cohort 2) 10 mg/kg (Cohort 3)	PBO Randomized/completed: 7/5 Sex: 1M/4F Race: 5 JP *APOE4* carrier: 3Y, 2N	Immediately before infusion, 1, 2, 3, 5, 25 hours from start of infusion, Day 5, Day 8, Day 15, Day 22, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 100, Day 113, Day 155, Day of withdrawal, 56 days after the last dose.
			LEC2.5 Randomized/completed: 6/6 Sex: 4M/2F Race: 6 JP *APOE4* carrier: 4Y, 2N	
			LEC5 Randomized/completed: 6/6 Sex: 3M/3F Race: 6 JP *APOE4* carrier: 5Y, 1N	

Study Number	Study Design/Population	Lecanemab Dose Regimen	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
			LEC10 Randomized/completed: 7/7 Sex: 5M/2F Race: 7 JP *APOE4* carrier: 4Y, 3N	
BAN2401-A001-004 (Study 004) Total sites: 1	Open-Label, Parallel-Group, Randomized Study to Evaluate the Absolute Bioavailability of Single Dose Subcutaneous Administration of Lecanemab in Healthy Subjects ≥18 and ≤65 years old	10 mg/kg (IV) (Treatment A) Fixed 700 mg SC (Treatment B)	LEC10 (IV) Randomized/completed: 30/30 Sex: 20M/10F Race: 17W, 8B, 5A	IV and SC Day 1 at predose and postdose at 1 (IV: end of intravenous infusion and SC: 1-hour postdose), 2, 4, 8 hours, and on Day 2, Day 3, Day 4, Day 5, Day 6, Day 8, Day 15, Day 22, Day 29, Day 36, Day 50, and any ET
			LEC 700 (SC) Randomized/completed: 30/29 Sex: 18M/11F Race: 16W, 9A, 4B	
BAN2401-A001-005[a] (Study 005)	Open-label, parallel group, single site; randomized study to evaluate the bioequivalence of single dose SC formulation of lecanemab supplied in vials and a single use AI in healthy volunteers	LEC 720 (SC) vial LEC 720 (SC) vial AI	NA	Day 1 at predose, postdose at 4 and 8 hours, and on Day 2, Day 3, Day 4, Day 5, Day 6, Day 8, Day 15, Day 22, Day 29, Day 36, Day 50, and any ET visit as applicable.

Study Number No. of Sites: Countries	Study Design/Population	Lecanemab Dose	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
BAN2401-G000-201 Core (Study 201 Core) Total sites: 117	Double–blind, parallel-group, placebo-controlled, multicenter and multinational study utilized a dose-finding RAR design to evaluate the safety, tolerability, and efficacy of lecanemab in subjects with MCI due to AD – intermediate likelihood, or with mild AD (collectively designated as EAD) aged 50 to 90 years	2.5 mg/kg biweekly (LEC2.5-BW) 5 mg/kg monthly (LEC5-M) 5 mg/kg biweekly (LEC5-BW) 10 mg/kg monthly (LEC10-M) 10 mg/kg biweekly (LEC10-BW)	Placebo Randomized[a]/completed: 247/177 Sex: 107M/138F Race: 222W, 5B, 10JP, 6OA, 1CN, 1O *APOE4* carrier: 174Y (40HO, 134HET), 71N Clinical Subgroup: 159MCI, 86Mild AD	Core At Week 1, approximately 4 hours after the end of infusion (before subjects leave the clinic for home), at Weeks 13, 27, 39, 53, 65, and 77 blood was taken at predose and at least 2 hours after the end of infusion, Early Termination and Unscheduled Visits.
			LEC2.5-BW Randomized/completed: 52/35 Sex: 26M/26F Race: 48W, 2B, 1JP, 1OA *APOE4* carrier: 38Y (5HO, 33HET), 14N Clinical Subgroup: 34MCI, 18Mild AD	
			LEC5-M Randomized/completed: 51/37 Sex: 24M/26F Race: 46W, 1B, 1OA *APOE4* carrier: 40Y (12HO, 28 HET), 11N Clinical Subgroup: 36MCI, 15Mild AD	

Study Number No. of Sites: Countries	Study Design/Population	Lecanemab Dose	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
			LEC5-BW Randomized/completed: 92/61 Sex: 42M/50F Race: 73W, 4B, 6JP, 3OA, 3O *APOE4* carrier: 84Y (14HO, 70HET), 8N Clinical Subgroup: 53MCI, 39Mild AD	
			LEC10-M Randomized/completed: 253/155 Sex: 141M/112F Race: 228W, 5B, 12JP, 5OA, 3O *APOE4* carrier: 225Y (60HO, 165HET), 28N Clinical Subgroup: 170MCI, 83Mild AD	
			LEC10-BW Randomized/completed: 161/87 Sex: 91M/70F Race: 150W, 4B, 5JP, 2OA *APOE4* carrier: 49Y (10HO, 39HET), 112N Clinical Subgroup: 95MCI, 66Mild AD	

Study Number No. of Sites: Countries	Study Design/Population	Lecanemab Dose	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
BAN2401-G000-201 Open-label extension (Study 201 OLE Phase, Ongoing) Total: 59 sites	OLE Phase to Study 201	LEC10-BW (IV)	LEC10-BW Enrolled/treated: 180/180 Sex: 93M/87F Race: 148W, 2B, 30A (including 21JP, 1CN, 8SK) *APOE4* carrier: 125Y (28HO, 97HET), 55N Clinical Subgroup at the start of Core: 110MCI, 70Mild AD	Extension At Week [redacted], at Weeks [redacted], and [redacted] blood was taken predose and [redacted]. Also, at Early Termination, Follow-up, and Unscheduled Visits.

Study Number No. of Sites: Countries	Study Design/Population	Lecanemab Dose	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
BAN2401-G000-201 Open-label extension (Study 201 OLE Phase, Ongoing) Total: 59 sites	OLE Phase to Study 201	LEC10-BW (IV)	LEC10-BW Enrolled/treated: 180/180 Sex: 93M/87F Race: 148W, 2B, 30A (including 21JP, 1CN, 8SK) *APOE4* carrier: 125Y (28HO, 97HET), 55N Clinical Subgroup at the start of Core: 110MCI, 70Mild AD	Extension At Week 1 (4 hours after the end of infusion), at Weeks 3, 9, 13, 27, 39, 53, 79, 105, 131, 157, 183, 209, 235, and 261 blood was taken predose and at least 2 hours after the end of infusion. Also, at Early Termination, Follow-up, and Unscheduled Visits.

Study Number No. of Sites: Countries	Study Design/Population	Lecanemab Dose	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
BAN2401-G000-301 (Study 301 Core) Total sites: 235	Double-blind, parallel-group, placebo-controlled, multicenter study to confirm the safety and efficacy of lecanemab in subjects with EAD (MCI) due to AD with intermediate likelihood/prodromal AD or mild AD and confirmed amyloid pathology indicated by positive amyloid load aged 50 to 90 years, inclusive	PBO (IV) LEC10-BW (IV)	Randomized/completed: 1795/1486 Sex: 857M, 938F Race: 1381W, 303A, 47B, 33O, 28MI, 2NAM, 1NH	Week 1 (4 hours after the end of infusion), predose and at least 2 hours after the end of infusion at Weeks 5, 13, 27, 39, 53, 65, 77, and 79a; Early termination, 3-month Follow-up Visit, and Un-Scheduled Visit.
BAN2401-G000-301 Open-label extension (Study 301 OLE Phase, Ongoing) Total sites: 184	OLE Phase to 301	LEC10-BW (IV) (or 720 mg SC as a weekly dose in optional substudy; SC data not included in this submission)	Treated/completed: 964/38 Sex (LEC10-BW treated population, including Core LEC10-BW subjects): 667M, 724F Race: 1056W, 249A, 35B, 2O, 21MI, 1NAM	Predose and at least 2 hours after the end of infusion at Weeks 79, 93b, 105, 117, 133, and 157, Week 179, Early termination visit, 3 month follow-up and unscheduled visit
BAN2401-G000-303 (Study 303, Ongoing) Total sites: 102	Study 303 consists of 2 trials (A45 and A3) under a single protocol and is a double-blind, parallel treatment arm, placebo-controlled study to evaluate efficacy and safety of treatment with lecanemab in subjects with preclinical AD and elevated amyloid (A45 Trial) and subjects with early preclinical AD and intermediate Amyloid (A3 Trial) aged 55 to 80 years.	A45 PBO (IV) or LEC5-BW (IV) through 8 weeks (titration), then LEC10-BW (IV) through 96 weeks (induction), then LEC10 M (IV) through 216 weeks (maintenance) A3 PBO (IV), or LEC5 M (IV) through 8 weeks (titration), then LEC10 M (IV) through 216 weeks	Randomized: 322 subjects had been randomized (223 subjects in the A45 Trial, and 99 subjects in the A3 Trial). Demographics not available.	A45 Predose, 4 hours after the 1st infusion, and at any time postdose at Weeks 4, 12, and 24; predose at Weeks 48 and 96, Early Termination, Follow-up, and Unscheduled visit A3 Predose and approximately 4 hours after the end of infusion at Weeks 0, 4, 12, and 24; predose at Weeks 48 and 96, Early Termination (predose), Follow-up, and Unscheduled visit

Study Number No. of Sites: Countries	Study Design/Population	Lecanemab Dose	Total No. of Subjects Randomized/Completed Sex, Race	PK Sampling Schedule
Phase 2/3 Studies: Subjects with Dominantly-Inherited AD				
DIAN-TU-001[c] (Ongoing)	A Phase 2/3 Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited AD	10 mg/kg (IV) 720 mg (SC)	No data to report	Symptomatic Cohort 1 Predose at Week 12, Week 24, Week 52, Week 76, Week 104, Week 128, Week 156, Week 180, Week 208, Week 260, Week 312, Week 364. Asymptomatic Cohort 2 Predose at Week 76, Week 104, Week 128, Week 156, Week 180, Week 208, Week 260, Week 312, Week 364.

A = Asian, AD = Alzheimer's disease, B = Black or African American, EAD = early Alzheimer's disease, IV = intravenous, F = female, LEC5-BW = lecanemab 5 mg biweekly, LEC5-M = lecanemab 5 mg monthly, LEC10-BW = lecanemab 10 mg biweekly, LEC10-M = lecanemab 5 mg monthly, M = male, MCI = mild cognitive impairment, MI = missing, NAM = American Indian or Alaskan Native, NH = Native Hawaiian or Other Pacific Islander, O = other, OLE = open-label extension, PBO = placebo, PK = Pharmacokinetic, SC = subcutaneous, W = White.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Lecanemab in serum was measured by two different methods, an ELISA method (TCAR10-120), and a LC-MS/MS method (BTM-1425-R0), well validated. Both methods were used for Study 101, and bridging is discussed in this study. Both methods appear acceptable.

Immunogenicity of lecanemab was evaluated using a tiered approach. Immunogenicity was first assessed using a validated anti-drug antibody (ADA) based on the electrochemiluminescence (ECL) meso scale discovery platform. ADA confirmed positives were assessed in a neutralizing antibody assay (NAB), a non-cell-based competitive ligand binding neutralisation ECL immunoassay.

PK, PKPD, and ER analyses were performed using modelling and simulation techniques. Population PK, PKPD, and ER modelling exercises are described in overall seven reports which are summarised and discussed in this section below (PK only of reports CPMS-BAN2401-002R-v1.1 and CPMS-BAN2401-002R-ADD1-v1).

Population PK models were developed using pooled data from two Phase 1, one Phase 2, and one Phase 3 study (BAN2401-A001-101, BAN2401-J081-104, BAN2401-G000- 201 CORE and OLE, and BAN2401-G000-301 CORE and OLE). Generally applied methods for model evaluation and qualification were used.

Absorption

The influence of formulation (Process A-1 versus Process B-1) was investigated during population PK model development. The relative bioavailability (F1) for Process B-1 was estimated at 0.904 (IIV = 8.51 %CV). Comparison of formulations A1 vs. B1 and A1 vs. C1 are provided, and satisfactory. However, no comparison is provided with to-be marketed formulation C2.

Study 004 was designed to compare IV vs. SC bioavailability. It is less relevant for this application and will not be developed further.

For exposure, results of study 104 are displayed below and PK parameters are displayed in the target population section.

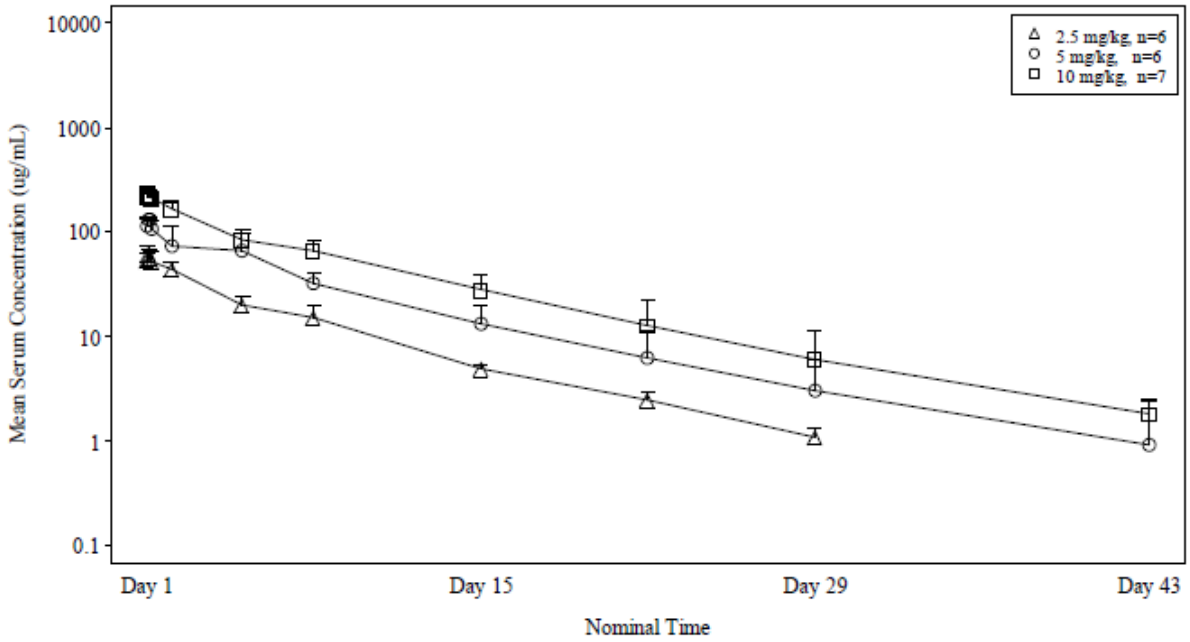


Figure 2. Study 104, mean and SD concentration-time curve of lecanemab after single administration

Distribution

Based on population PK modelling, the estimated volume of distribution of the central compartment is 3.24 L (IIV = 12.2 %CV) and of the peripheral compartment 2 L (IIV = 94.6 %CV).

Interaction with plasma proteins is not expected. Study 101 showed the highest CSF / plasma concentration ratios were observed at D85, suggesting slow diffusion during serum elimination phase.

Elimination

Lecanemab elimination occurs through normal degradative pathways for immunoglobulins.

Based on population PK modelling, the estimated clearance (CL) is 0.0154 L/h (IIV = 34.9 %CV)

In studies 101 and 104, T1/2 was 5.5 to 7.3 days. CL found in Study 104, with means of 0.0217 to 0.0239 L/h if assuming an average weight of 70 Kg.

Dose proportionality and time dependencies

Both studies 101 and 104 show dose-proportional exposures of lecanemab in the 0.3 to 15 mg/kg range.

In study 101, in the 10 mg cohort, accumulation ratio was 1.39; no change of T1/2 or signs of time dependency were observable in the MAD section.

In Study 104, Rac(AUC) was around 1.50 among all three dose levels. After starting multiple dose administrations once every 2 weeks, the steady state was achieved after the 4th dose.

Table 2. Study 104, point estimate of b and 95% CI after first dose

PK Parameter	Point Estimate of b	95% Confidence Interval of b Lower Limit, Upper Limit
C_{max} (µg/mL)	0.939	0.807, 1.07
$AUC_{(0\text{-}inf)}$ (µg•h/mL)	1.06	0.819, 1.31

Pharmacokinetic Analysis Set: (N=19)

$AUC_{(0\text{-}inf)}$ = area under the concentration-time curve from zero time extrapolated to infinite time, C_{max} = maximum observed concentration, PK = pharmacokinetic.

Source: Table 14.2.2.3

Table 3. Study 104, point estimate of b and 95% CI after last dose

PK Parameter	Point Estimate of b	95% Confidence Interval of b Lower Limit, Upper Limit
$C_{ss,max}$ (µg/mL)	1.03	0.860, 1.21
$AUC_{(0\text{-}\tau)}$ (µg•h/mL)	1.07	0.854, 1.28

Pharmacokinetic Analysis Set: (N=19)

$AUC_{(0\text{-}\tau)}$ = area under the concentration-time curve over the dosing interval on multiple dosing, $C_{ss,max}$ = maximum observed concentration at steady state, PK = pharmacokinetic.

Pharmacokinetics in target population

A model was developed using Phase 1, 2, and 3 data, including the data collected in the pivotal Phase 3 study (report CPMS-BAN2401-003R1-v1). The final for lecanemab is a 2-compartment model with zero-order input and first-order elimination from the central compartment. The bioavailability (F1) of Process B-1 relative to Process A-1 is included (F1=0.904). IIV on CL (0.0154 L/h, IIV=34.9 %CV), V1 (3.24 L, IIV=12.2 %CV), V2 (2 L, IIV=94.6 %CV), and F1 (IIV = 8.51 %CV) are included. Statistically significant covariate effects of ADA status (time-variant; estimate=1.13), body weight (exponent=0.353), albumin (exponent=-0.374), and sex (estimate=0.791) on CL; sex (estimate=0.868), Japanese race/ethnicity (estimate=0.920) and body weight (exponent=0.513) on central volume of distribution, and Japanese race/ethnicity on peripheral volume of distribution (estimate=0.671) were identified.

PK parameters after multiple doses in study 104 are presented below.

Table 4. Study 104, summary of PK parameters of lecanemab after multiple administration once every 2 weeks at last dose

PK Parameter	BAN2401		
	2.5 mg/kg (n=6)	5 mg/kg (n=5)[a]	10 mg/kg (n=6)[b]
$C_{ss,max}$ (µg/mL)	72.8 (19.4)	154 (26.3)	299 (45.7)
$t_{ss,max}$ (h)	1.150 (1.03, 2.15)	1.920 (0.95, 2.83)	2.010 (1.00, 4.90)
$AUC_{(0-24h)}$ (µg•h/mL)	1380 (268)	3050 (486)	5830 (887)
$AUC_{(0-\tau)}$ (µg•h/mL)	8980 (1690)	22700 (7790)	39500 (7330)
$R_{ac}(C_{max})$[c]	1.12 (0.0757)	1.17 (0.189)	1.31 (0.143)
$R_{ac}(AUC)$[d]	1.45 (0.136)	1.51 (0.348)	1.59 (0.220)

Pharmacokinetic Analysis Set: (N=19)
Data are shown as mean (SD) except $t_{ss,max}$; for $t_{ss,max}$, median (min, max) is shown.
$AUC_{(0-24h)}$ = area under the concentration-time curve from zero (predose) to fixed time-point 24 h, $AUC_{(0-\tau)}$ = area under the concentration-time curve over the dosing interval on multiple dosing, $C_{ss,max}$ = maximum observed concentration at steady state, max = maximum, min = minimum, PK = pharmacokinetic, $R_{ac}(AUC)$ = accumulation ratio based on AUC, $R_{ac}(C_{max})$ = accumulation ratio based on C_{max}, $t_{ss,max}$ = time at which the highest drug concentration occurs at steady state.
a: One of 6 subjects in 5 mg/kg group was excluded from noncompartmental analysis because the 6th dose was not administered.
b: One of 7 subjects in 10 mg/kg group was excluded from noncompartmental analysis because the 6th dose was not administered.
c: $R_{ac}(C_{max}) = C_{ss,max}$ (after the 6th dose)/C_{max} (after the 1st dose)
d: $R_{ac}(AUC) = AUC_{(0-\tau)}$ (after the 6th dose)/$AUC_{(0-336h)}$ (after the 1st dose)

Special populations

- *Impaired renal function*

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

- *Impaired hepatic function*

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

- *Gender*

Among the study population (n=1619), overall 800 (49.4 %) were female and 819 (50.6 %) male. Sex was identified as a statistically significant covariate on CL (estimated ratio=0.791) and V1 (estimated ratio=0.868).

- *Race/ethnicity*

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

- *Body weight*

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

- *Elderly / Age*

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

- *Children*

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

- *Albumin level*

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

- *Immunogenicity*

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

2.6.2.2. Pharmacodynamics

Mechanism of action

Lecanemab, also known as BAN2401, is a humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody that preferentially binds with highest affinity to large soluble amyloid beta (Aβ) protein aggregates, known as protofibrils, while maintaining high affinity for fibrillar Aβ that are a major component of Aβplaques. The accumulation of Aβ plaques in the brain is a defining pathophysiological

feature of Alzheimer's disease (AD). Lecanemab is being developed as a treatment for AD, with this submission intended to support registration of lecanemab for the treatment of mild cognitive impairment (MCI) due to AD and mild AD, a population collectively described as early AD (EAD).

Lecanemab distinguishes itself from other anti-amyloid mAbs, in that it selectively targets large soluble protofibrils relative to monomers (greater than 1000-fold selectivity over Aβ monomers), with preferential activity over insoluble fibrils. Lecanemab is therefore intended to have much greater relative activity against the hypothesised primary toxic amyloid species implicated in AD pathology. The effect of lecanemab to reduce brain amyloid was measured using amyloid positron emission tomography (PET) imaging. Since clearance (CL) of brain amyloid may alter the dynamics of Aβ aggregation and result in changes in levels of total Aβ monomers, changes in Aβ levels were also explored in plasma to support target engagement of lecanemab. Evidence of drug-related effect on downstream AD pathophysiology was further explored using biomarkers, including plasma human tau protein phosphorylated at threonine in position 181 (p-tau181) as a biomarker of tau pathology. The intended effect would be a reduction or slowdown of accumulation of these pathophysiological biomarkers that are downstream of brain amyloid pathology.

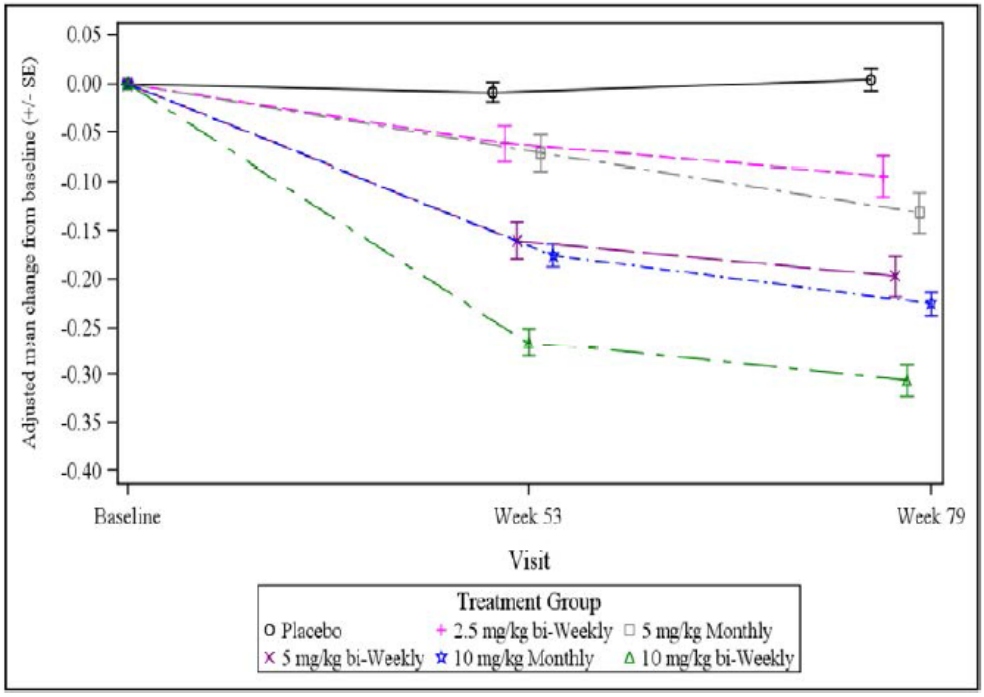
Primary and secondary pharmacology

Primary pharmacology

The primary objective of the Phase 3 Study 301 Core was to confirm the efficacy of lecanemab in subjects with EAD by determining the superiority of lecanemab compared with PBO on the change from baseline in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) at 18 months of treatment. The LEC10-BW dosing regimen chosen for Study 301 was based on the large dose-range finding Study 201, which suggested that this dosing regimen most effectively removed brain amyloid load (as determined by amyloid PET) with a safety profile that was deemed to be acceptable, especially with regards to infusion reactions and ARIA-E. The results from Study 201 are presented below.

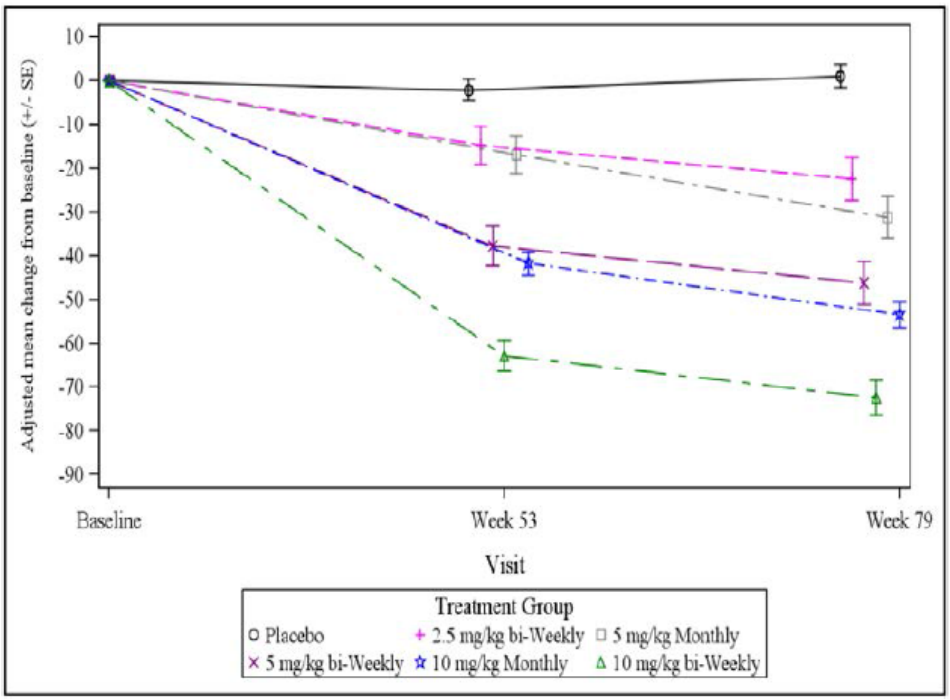
Figure 3 present the reduction in least square mean CFB in brain amyloid levels as measured by amyloid PET SUVr over 18 months.

Figure 3. Least square mean (± SE) change from baseline in brain amyloid levels as measured by amyloid PET SUVr normalised to whole cerebellum mask by visit – study 201 core (PD analysis set)



The PET SUVr results using the whole cerebellum (WC) reference region were also recalculated to the centiloid scale. The results are presented with the centiloid scale to help compare brain amyloid reduction results between different tracers (Figure 4).

Figure 4. Least square mean (± SE) change from baseline in brain amyloid levels as measured by amyloid PET in centiloid scales by visit – study 201 core (PD analysis set)



See also the below section on relationship between plasma concentration and effect.

Secondary pharmacology

The applicant did not provide a separate discussion with regards to the secondary pharmacology effects of lecanemab. At the time of the MAA, one study included healthy volunteers (BAN2401-A001-004) to evaluate the absolute bioavailability of single dose subcutaneous administration of lecanemab. Available safety results in healthy volunteers and phase I studies are summarised in each sub section of safety part of the clinical assessment below.

Relationship between plasma concentration and effect

The relationship of lecanemab exposure with different PD (bio)markers in Phase 2 study BAN2401-G000-201 and Phase 3 Study BAN24-01-G000-301 were investigated using different modelling approaches.

An Emax ER model, with lecanemab concentrations in CSF as the measure of exposure, best described the CSF Aβ1- 42% change from baseline.

Disease progression models for efficacy measures (ADCOMS, CDR-SB, ADAS-Cog, and MMSE) were linked to lecanemab exposure (Css,av) suggesting linear relationship with exposure. However, the modelling results appear to be not in line with the visual inspection of the data, where no relationship between exposure and change from baseline in efficacy markers would be seen.

A logistic regression was applied to describe the relationship with safety (ARIA-E) suggesting an increase in ARIA-E events with increasing exposure, and higher incidences for *APOE4* carriers. Isolated ARIA-H events were not modelled due to lack of relationship with exposure.

A change in amyloid PET (SUVr and centiloid units) appears to be correlated with treatment, particularly within the first 500 days compared to placebo, leading to a decrease in amyloid PET over time.

A correlation between serum lecanemab exposure and plasma Aβ42/40 ratio as well as p-tau181 can be observed and was described with indirect response models showing an increase in plasma Aβ42/40 ratio and decrease in plasma p-tau181 with treatment. Slight differences can be observed between doses.

The relationships between amyloid PET, plasma Aβ42/40 ratio and plasma p-tau181 with CDR-SB and ADCOMS (and ADAS-Cog14 for amyloid PET and p-tau181) were described as well, suggesting linear relationships and reduction in disease progression with lecanemab treatment.

Moreover, plasma Aβ42/40 ratio and plasma p-tau181 appear to be correlated with amyloid PET (SUVr).

2.6.3. Discussion on clinical pharmacology

Time dependency and dose proportionality

Both studies 101 and 104 show dose-proportional exposures of lecanemab in the 0.3 to 15 mg/Kg range. Accumulation ratio can be considered as 1.39, and there was no sign of time dependency.

Immunogenicity

The ADA assay utilised to analyse the immunogenicity of lecanemab in clinical studies has a limited drug tolerance, i.e. 31.3 µg/mL lecanemab for detecting 100 ng/mL ADAs. This is insufficient, as a

substantial proportion of the ADA samples in the clinical studies have lecanemab serum concentration above this threshold. The Immunogenicity of lecanemab has therefore not been evaluated adequately. The applicant has committed to improve the assay and analyse samples from the study 301 Core.

New immunogenicity data from the improved assays was proposed by the applicant to be submitted in late 2025. With the new data the impact of immunogenicity on efficacy, safety and PK should be re-evaluated by applicant (as PAM). The applicant confirmed the commitment to reanalyse the Study 301 Core samples in late 2025 using an improved ADA assay (drug tolerance limit of 1000 µg/mL of lecanemab with 100 ng/mL ADA).

Pharmacodynamics and PK/PD

Visual inspection of change from baseline score CDR-SB and ADAS-Cog14 by lecanemab exposure quartiles appear not to show a difference for different higher $C_{ss,av}$ compared to lower exposures, suggesting a lack of relationship between exposure and change from baseline score. Disease progression models of model-predicted lecanemab exposure with efficacy measures of CDR-SB (primary endpoint in pivotal Phase 3 study) and ADAS-Cog14 (key secondary endpoint in pivotal Phase 3 study) change from baseline at 18 months were developed. These models were developed using data from BAN2401-G000-201 and BAN2401-G000-301 CORE and OLE. Linear disease progression models with several IIVs and covariates were selected as final models with lecanemab $C_{ss,av}$ as exposure metric. Based on the modelling findings, a linear relationship of lecanemab $C_{ss,av}$ with decrease in disease progression rate is claimed. However, this appears not to be in line with the provided graphs where no relationship between exposure and change from baseline score is observed. In addition, as can be observed from the presented VPCs, changes from baseline score over time appear similar between placebo and lecanemab treated patients. Results from this model require cautious interpretation.

A key secondary endpoint in the pivotal Phase 3 trial was the change from baseline in amyloid PET (centiloids) at 18 months. An indirect response PKPD model of lecanemab exposure and brain amyloid PET centiloid (and SUVr) using data from studies BAN2401-G000-201 and BAN2401-G000-301 CORE and OLE was developed. Based on these results, APOE4 carrier patients appear to have higher baseline amyloid PET and older patients are expected to experience a higher lecanemab drug effect. A similar model was also developed for amyloid PET (centiloids) using Phase 2 data only. It appears that these models are able to sufficiently describe the reduction in amyloid PET centiloid over time under treatment with lecanemab. Based on this model, about 56.9% of patients are expected to achieve amyloid negativity for centiloid (<30.0) after 18 months. It seems that a difference in centiloid PET can be observed, particularly within the first 500 days for lecanemab treated (10 mg/kg biweekly) compared to placebo.

Study BAN2401-G000-201 CORE data were used for disease progression modelling of lecanemab exposure with ADCOMS as efficacy measure. A linear model with $C_{ss,av}$ was used here as well. Concomitant AD treatment and diagnosis on baseline clinical score were identified as covariates. The model seems to be able to sufficiently describe the data. The results suggest a benefit from treatment with lecanemab compared to placebo in terms of less progression (here reduction in ADCOMS from baseline).

The relationship between model-predicted serum lecanemab concentration and Aβ42/40 ratio was described by an indirect response model with a linear function and for p-tau181 with an Emax function. Aβ42/40 ratio baseline was 5% higher in Japanese, 1% higher in females, 2.5% lower in ADA positive patients and decreased with an increase in age. For the p-tau181 model covariates were identified for body weight, baseline MMSE and *APOE4* carrier status on baseline. There seem to be a slight increase in plasma Aβ42/40 ratio and decrease in plasma p-tau181 after treatment with 10 mg/kg lecanemab

biweekly compared to placebo. Both plasma markers appear to be correlated with a change from baseline in amyloid PET SUVr, i.e. reduction from baseline.

None of the efficacy models indicated a large impact of exposure on efficacy measures CDR-SB and ADAS-Cog14. Exposure had influence on ARIA-E incidence for subjects with genotype APOE4 and especially for APOE4 homozygous subjects. There was no correlation between exposure and isolated ARIA-H monitored in Study 301 Core.

APOE4 homozygous carriers have high risk for ARIA-E (about 1 in 3 treated 10 mg/kg biweekly lecanemab). The Applicant was requested to discuss risk mitigation for ARIA-E including dose reduction for APOE4 carriers. APOE4 carriers should not be subject to more risk for ARIA events than APOE4 non-carriers. An exposure limit could be defined from the exposure observed in APOE4 non-carriers. Pop PK simulations could be used to select appropriate doses for the specific APOE4 genotypes to maintain exposure within the exposure range observed for APOE4 non-carriers, which could include dose capping for over-weight patient**.** The Applicant evaluated that a 3-fold lower dose for APOE4 homozygous subjects would reduce the risk for ARIA incidences to the level observed for APOE4 non-carriers, but it would result in a non-efficacious treatment. The Applicant highlights that APOE4 genotype is the predominant risk factor for ARIA-E incidence. This is agreed. Risk for ARIA-E incidence also increase with body weight (Figure 7), but to a lesser extent. Thus, it can be concluded that dose is a risk factor, mainly to subjects with homozygous APOE4 carrier status. The figure below indicates the increased risk for ARIA-E is Cmax driven and thus a lower dose for APOE4 homozygote population is warranted.

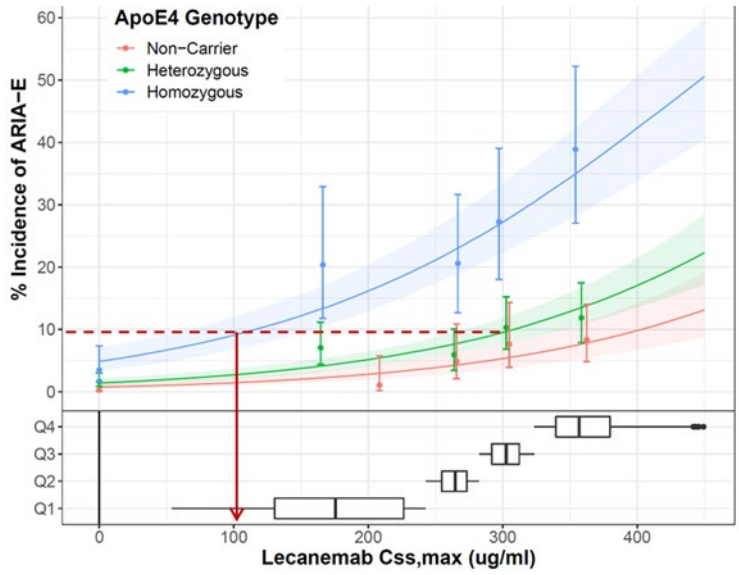


Figure 5. Css,max vs incidence of ARIA-E

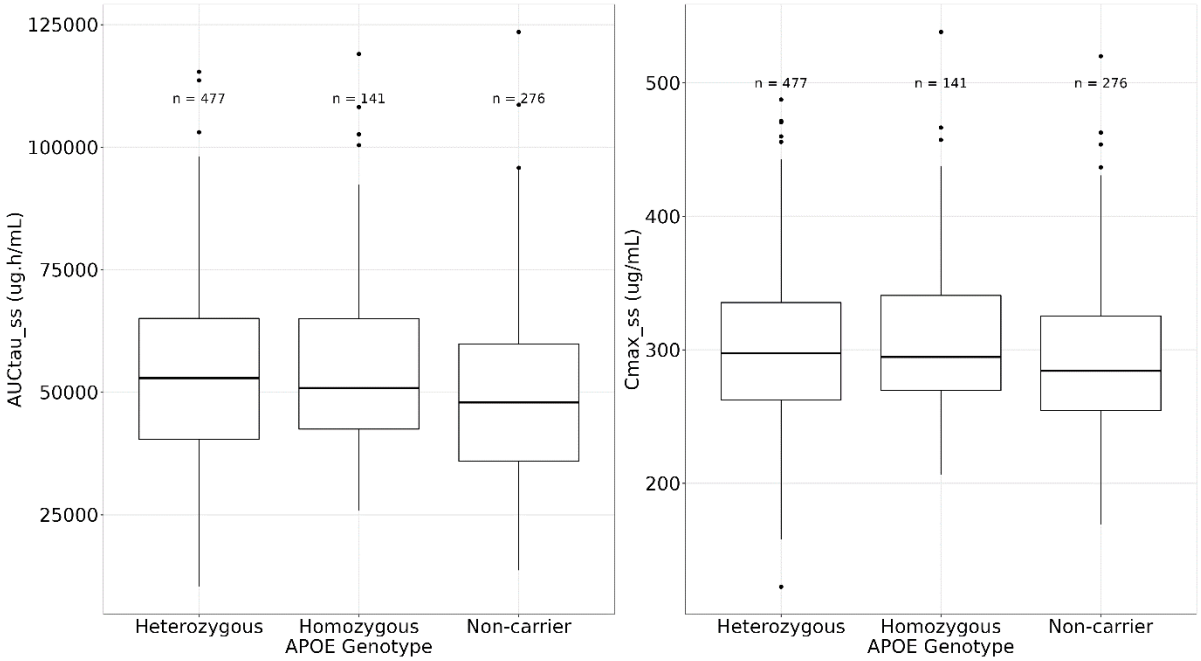


Figure 6. Steady state AUCtau and Cmax using pk148 model stratified by APOE4 genotype in study 301 core

APOE4 = apolipoprotein E4 variant, AUC_{tau_ss} = area under the concentration curve between dosing intervals at steady state, $C_{ss,max}$ = maximum concentration at steady state.

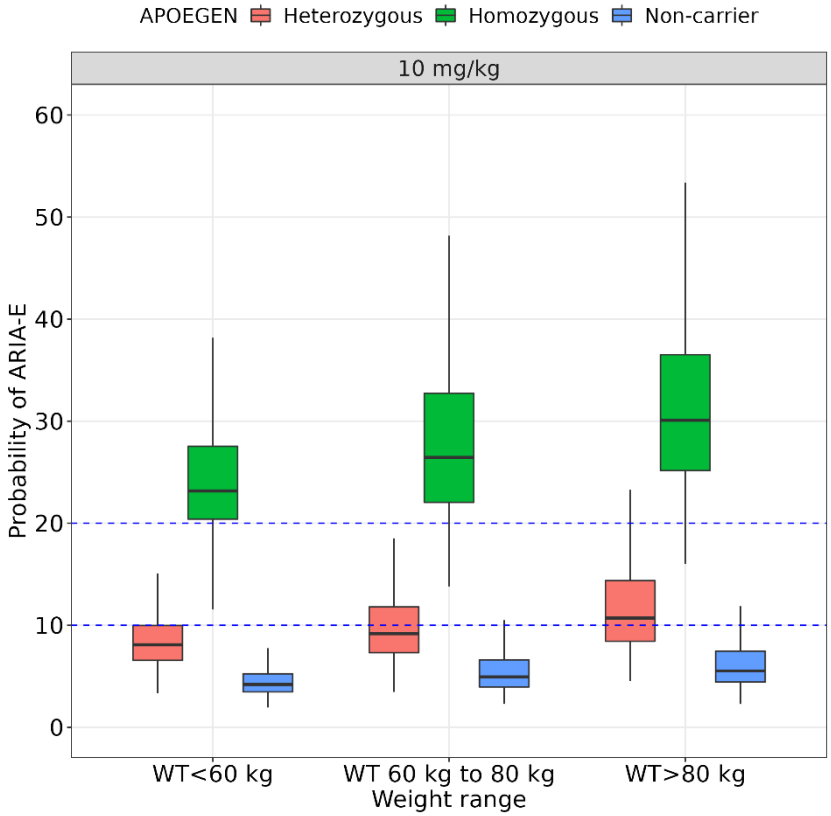


Figure 7. Model-predicted ARIA-E incidence across bodyweight ranges

APOE4 = E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion.

The 10 mg/kg biweekly dose regimen is not considered acceptable for subjects with homozygous APOE4 carrier status (see also efficacy and safety sections below). The Applicant states "[s]ince doses below 10 mg/kg did not demonstrate efficacy, dose reduction for homozygous subjects is not feasible". This statement is not agreed. Dose-response results of long-term treatment of APOE4 homozygous subjects indicate no relevant difference between 2.5 mg/kg BW dosing and 10 mg/kg BW dosing regimens across 3 different score markers of Alzheimer's disease. In summary, APOE4 homozygous carriers have an unacceptably high risk for ARIA-E with the proposed 10 mg/kg dose. The risk seems Cmax driven. These patients also have less or no benefit with the investigated lecanemab dose compared to subjects with heterozygous APOE4 carrier or non-carrier status. The Applicant could not propose a justified dose-reduction with any expectation of efficacy. Aside from the overall evaluations on the benefit/risk (see sections below), the higher risk of ARIA-E defines the APOE4 homozygous carriers as a population of even greater concerns. In the same vein, the SAG-N experts agreed by consensus that heterozygous and even more homozygous ApoE4 carriers are a group of higher risk of adverse events. As a consequence – had the b/r been positive in the complementary population (which is not the case) - genotyping should have been mandatory and lecanemab 10 mg/kg biweekly should have been contraindicated for APOE4 homozygous carriers (about 15% of AD population), as also agreed by the SAG-N experts by consensus.

Upon request, the applicant accepted to strengthen the warning – in the proposed SmPC - for ARIAs in subjects with homozygous APOE4 carrier status, to include the model predicted ARIA-E incidences as follows: "Model predicted risk of ARIA-E, including symptomatic and serious ARIA, is increased approximately 3- or 6-fold in apolipoprotein E ε4 (ApoE ε4) homozygotes carriers compared to APOE ε4 heterozygotes carriers or non-carriers, respectively".

The incidence of ARIA-E as a function of lecanemab exposure ($C_{ss,max}$) was modelled with the logit function, which seems to fit the data generally. A higher incidence is observed in *APOE4* carriers compared to non-carriers. The incidence of ARIA-E seems highest in *APOE4* homozygous carriers and lowest in non-carriers. In addition, time to the first event of ARIA-E as a function of lecanemab $C_{ss,max}$ was described by a hazard model. The incidence of isolated ARIA-H was assessed graphically and appear not to be correlated with any exposure measure.

2.6.4. Conclusions on clinical pharmacology

PK and PD appears of lecanemab appears sufficiently characterised from human data collected in particular, in one Phase 2 and one Phase 3 study.

A clear relationship between lecanemab exposure and change from baseline in CDR-SB and ADAS-Cog14 scores has not been clearly demonstrated.

The body weight dosing with the 10 mg/kg biweekly dosing appears a justified dose (however, see below for the benefit-risk discussion). No adequate dose could be found for homozygote APOE4 carrier status.

2.6.5. Clinical efficacy

The clinical efficacy development is mainly based on one dose finding Phase 2 study:

- BAN2401-G000-201 (Study 201) Core utilised a response-adaptive randomisation (RAR) design to evaluate the efficacy, safety, and tolerability of lecanemab in subjects with EAD. Study 201 evaluated doses of 2.5, 5, or 10 mg/kg given biweekly (LEC2.5-BW, LEC5-BW, LEC10-BW), or 5 or 10 mg/kg given monthly (LEC5-M, LEC10-M), or PBO for 18 months. The core phase was

followed by an open label phase (Open-label Extension (OLE)) evaluating a dose of LEC10-BW in all subjects.

and one pivotal Phase 3 study:

- BAN2401-G000-301 (Study 301) Core was a global, multicentre, double-blind, placebo-controlled, parallel-group study in subjects with EAD that evaluated LEC10-BW for 18 months to confirm the safety and efficacy of lecanemab. The core phase was followed by an open label phase (OLE) evaluating a dose of LEC10-BW in all subjects.

2.6.5.1. Dose response study(ies)

The clinical development included one dose finding Phase 2 study: BAN2401-G000-201.

This was a double–blind, parallel-group, placebo-controlled, multicentre and multinational study utilizing a dose-finding response adaptive randomisation design to evaluate the safety, tolerability, and efficacy of lecanemab in subjects with MCI due to AD (intermediate likelihood) or with mild AD dementia.

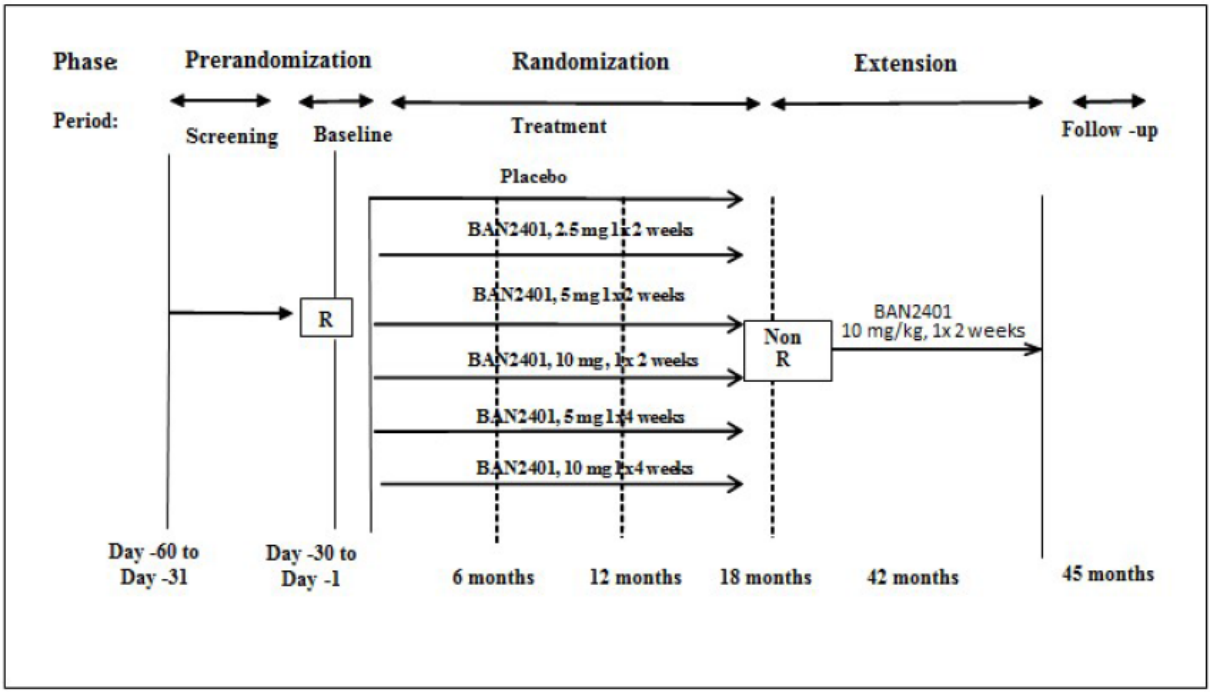


Figure 8. Design of study BAN2401-G000-201

Study population

Diagnosis

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

Key inclusion criteria

- Positive amyloid load as indicated by 1 of the following:

  a. PET assessment of imaging agent uptake into brain.

  b. CSF assessment of Aβ(1-42).

- Men and women aged between 50 and 90 years, inclusive.
- MMSE score equal to or greater than 22, and equal to or less than 30 at Screening and Baseline, except in France, Germany, Netherlands, Spain, Sweden, and United Kingdom, where the MMSE score was equal to or greater than 22 and equal to or less than 28 at Screening and Baseline.

Objective and Endpoints

Primary Objectives

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

Primary endpoint

- Change from Baseline at 12 months in ADCOMS.

Key Secondary endpoints

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

Treatment

The test drug was lecanemab (BAN2401) and the control was matching placebo. As shown in Table 5, there were a total of 6 treatment arms. Subjects were randomised to receive placebo or 1 of 5 doses of lecanemab (2.5, 5, or 10 mg/kg given biweekly, or 5 or 10 mg/kg given monthly) by IV infusion for the duration of the Randomisation Phase (18 months).

Table 5. Study treatments administered

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

ApoE4 = apolipoprotein ϵ4 variant.
a: Subjects who received study drug at 4-week intervals (monthly) received placebo at the intervening 2-week time points.
b: Subjects confirmed as ApoE4 carriers (homozygous or heterozygous) were not randomized to the 10 mg/kg 2-week interval (biweekly) dose after Protocol Amendments 04 and 05 (Sections 9.1 and 9.8.1).
Source: Appendix 16.1.1

Duration of Treatment

Core Study: Up to 18 months of treatment plus 3 months of follow-up.

Extension Phase: Up to 24 months of additional treatment plus 3 months of follow-up.

Statistics

Randomisation

A response adaptive randomisation (RAR) was used to allocate subjects to placebo control or 1 of the 5 active doses with the goal of characterizing the dose-response. Randomisation to placebo or one of five dose arms of BAN2401 was fixed for the first 196 subjects randomised in the study (4:2:2:2:2:2; placebo to each of the five active arms). Randomisation probabilities to each arm was then updated at each interim analysis such that the randomisation probability will be increased for the placebo arm and arms that represent the potential target dose (ED90) and simultaneously decreased for other active arms.

Analysis

The primary endpoint was analysed using prespecified Bayesian methods. Type I error was evaluated through Bayesian simulations by the probability of trial success in the scenario that there is no treatment effect. In the "Null" scenario, there is a 10% probability of trial success. This was – a priori - the 1-sided Type I error rate of this trial assuming a 20% dropout rate at 12 months. In case the dropout rate is 30% and 40%, the corresponding simulated type I error rate was 10.6% and 12.5%, respectively.

Where conventional analyses are also reported, all statistical tests for those will be based on the two-sided 10% or one-sided 5% level of significance.

Conduct of the study

There were 149 sites in North America (93), Europe (34), and Asia-Pacific (22).

Study Period

20 Dec 2012 (date of first subject's signed informed consent) through 19 Jul 2018 (21-month data Core Study).

Subject Disposition

Table 6. Numbers of subjects randomised to treatment

Treatment Arm	Number Randomized		
Placebo	247		
BAN2401 2.5 mg/kg biweekly	52		Total randomized to BAN2401: N=609
BAN2401 5 mg/kg monthly	51		
BAN2401 5 mg/kg biweekly	92		
BAN2401 10 mg/kg monthly	253	Combined BAN2401 10 mg/kg treatment groups: N=414	
BAN2401 10 mg/kg biweekly	161		
Total	856		

Source: Table 14.1.1.2.1

During the study, emerging data from the study indicated that ApoE4 homozygous individuals on the highest dose of BAN2401 (10 mg/kg biweekly) have the highest risk of developing symptomatic amyloid–related imaging abnormalities with cerebral oedema (ARIA–E). Thus, the Drug Safety Monitoring Board (DSMB) for the study recommended that the highest dose of BAN2401 (10 mg/kg biweekly) no longer be administered to ApoE4 homozygous subjects, and this approach was implemented for all subsequent randomisations. Shortly thereafter, the sponsor has agreed, following interaction with regulators through the Voluntary Harmonisation Procedure (VHP), that subjects who are confirmed APOE4 positive (APOE4 hetero- or homozygous) not be randomised to the 10 mg/kg, biweekly dose.

Results

Demographic and baseline characteristics

Regarding baseline characteristics, ApoE4 genotype was imbalanced across treatment groups due to the randomisation restrictions.

Table 7. Key demographic and baseline characteristics – full analysis set

			BAN2401						
Category		Placebo (N=238)	2.5 mg/kg Biweekly (N=52)	5 mg/kg Monthly (N=48)	5 mg/kg Biweekly (N=89)	10 mg/kg Monthly (N=246)	10 mg/kg Biweekly (N=152)	Total (N=587)	Combined Total (N=825)
Age (year)[a]	n	238	52	48	89	246	152	587	825
	Mean (SD)	71.11 (8.892)	70.50 (8.257)	70.42 (7.514)	70.64 (7.446)	71.26 (7.455)	72.64 (8.777)	71.39 (7.907)	71.31 (8.198)
	Median	72.00	70.50	71.00	72.00	71.00	73.00	72.00	72.00
	Min, max	50.0, 89.0	50.0, 86.0	55.0, 84.0	52.0, 87.0	53.0, 90.0	51.0, 88.0	50.0, 90.0	50.0, 90.0
Age group, n (%)	<65 years	55 (23.1)	11 (21.2)	9 (18.8)	20 (22.5)	44 (17.9)	27 (17.8)	111 (18.9)	166 (20.1)
	≥65 to <80 years	144 (60.5)	35 (67.3)	35 (72.9)	60 (67.4)	168 (68.3)	94 (61.8)	392 (66.8)	536 (65.0)
	≥80 years	39 (16.4)	6 (11.5)	4 (8.3)	9 (10.1)	34 (13.8)	31 (20.4)	84 (14.3)	123 (14.9)
Sex, n (%)	Male	101 (42.4)	26 (50.0)	24 (50.0)	41 (46.1)	136 (55.3)	88 (57.9)	315 (53.7)	416 (50.4)
	Female	137 (57.6)	26 (50.0)	24 (50.0)	48 (53.9)	110 (44.7)	64 (42.1)	272 (46.3)	409 (49.6)
CDR-Global, n (%)	0.5	200 (84.0)	44 (84.6)	40 (83.3)	77 (86.5)	210 (85.4)	133 (87.5)	504 (85.9)	704 (85.3)
	1	38 (16.0)	8 (15.4)	8 (16.7)	12 (13.5)	13 (14.6)	19 (12.5)	83 (14.1)	121 (14.7)
ApoE4 carrier status, n (%)	Carrier	169 (71.0)	38 (73.1)	37 (77.1)	81 (91.0)	218 (88.6)	46 (30.3)	420 (71.6)	589 (71.4)
	Heterozygous	129 (54.2)	33 (63.5)	26 (54.2)	67 (75.3)	160 (65.0)	38 (25.0)	324 (55.2)	453 (54.9)
	Homozygous	40 (16.8)	5 (9.6)	11 (22.9)	14 (15.7)	58 (23.6)	8 (5.3)	96 (16.4)	136 (16.5)
	Non-carrier	69 (29.0)	14 (26.9)	11 (22.9)	8 (9.0)	28 (11.4)	106 (69.7)	167 (28.4)	236 (28.6)
Disease stage, n (%)	MCI due to AD	154 (64.7)	34 (65.4)	33 (68.8)	52 (58.4)	166 (67.5)	90 (59.2)	375 (63.9)	529 (64.1)
	Mild AD	84 (35.3)	18 (34.6)	15 (31.3)	37 (41.6)	80 (32.5)	62 (40.8)	212 (36.1)	296 (35.9)
AChEIs and/or memantine at Baseline, n (%)	No	110 (46.2)	24 (46.2)	23 (47.9)	33 (37.1)	115 (46.7)	73 (48.0)	268 (45.7)	378 (45.8)
	Yes	128 (53.8)	28 (53.8)	25 (52.1)	56 (62.9)	131 (53.3)	79 (52.0)	319 (54.3)	447 (54.2)

Primary analysis

- *Change from Baseline at 12 months in ADCOMS*

The pre-specified primary Bayesian Analysis on ADCOMS at 12 Months - presented below – did not meet its primary outcome.

Table 8. Bayesian analysis of ADCOMS at 12 months – full analysis set

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

ADCOMS = Alzheimer's Disease Composite Score, CSD = clinically significant difference, ED_{90} = dose regimen with at least 90% of the d_{max} treatment effect, Max = maximum, Pr = probability.
Source: Appendix 16.1.9

A conventional analysis on ADCOMS at 12 Months is presented below, in the full population and by ApoE4 and clinical status.

Table 9. Summary of MMRM analyses of change from baseline in ADCOMS at 12 months - full analysis set

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

The change from Baseline for each parameter in overall population was analyzed using the MMRM with treatment group/combined treatment group, visit, disease stage (MCI due to AD, mild AD dementia), ApoE4 status (carrier, non-carrier), presence or absence of concomitant AD treatment (AChEIs and/or memantine) at Baseline, region, treatment group-by-visit interaction as factors, and Baseline value as covariate. The mixed-effects model within each randomization stratum (subgroup) was similar and was reduced by removing corresponding stratification factor from the model in overall population. Subjects were censored at the time of initiation or change of AChEIs or memantine treatment regimens.
AChEIs = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ADCOMS = Alzheimer's Disease Composite Score, ApoE4 = apolipoprotein ϵ4 variant, LS = least square, MCI = mild cognitive impairment, MMRM = mixed-effects model with repeated measures.
Source: Table 14.2.1.5a and Table 14.2.1.5.1a

Table 10. Summary of MMRM analyses of change from baseline in ADCOMS at 12 months by ApoE4 status - full analysis set

Visit Strata Level Statistic	Placebo (N = 238)	BAN2401 2.5 mg/kg bi-Weekly (N = 52)	BAN2401 5 mg/kg Monthly (N = 48)	BAN2401 5 mg/kg bi-Weekly (N = 89)	BAN2401 10 mg/kg Monthly (N = 246)	BAN2401 10 mg/kg bi-Weekly (N = 152)
Week 53						
ApoE4 Positive						
n	149	30	34	66	160	12
Least Square Mean	0.972	1.114	0.985	0.857	0.739	0.199
SE	0.145	0.297	0.287	0.200	0.137	0.367
LS Mean Difference: Active Dose - Placebo		0.142	0.013	-0.115	-0.233	-0.773
90% Confidence Interval for Differences		-0.382, 0.666	-0.496, 0.522	-0.502, 0.272	-0.529, 0.063	-1.405, -0.141
p-value		0.656	0.966	0.624	0.195	0.044
ApoE4 Negative						
n	58	12	11	6	22	87
Least Square Mean	0.715	1.281	1.847	1.626	0.559	0.694
SE	0.226	0.473	0.510	0.650	0.354	0.196
LS Mean Difference: Active Dose - Placebo		0.566	1.132	0.911	-0.156	-0.021
90% Confidence Interval for Differences		-0.276, 1.408	0.229, 2.035	-0.205, 2.028	-0.822, 0.509	-0.475, 0.433
p-value		0.268	0.040	0.179	0.698	0.938

Table 11. Summary of MMRM analyses of change from baseline in ADCOMS at 12 months by clinical status - full analysis set

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

<u>Key Secondary endpoints</u>

The key secondary endpoints – all measured at 18 months – are shown below.

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

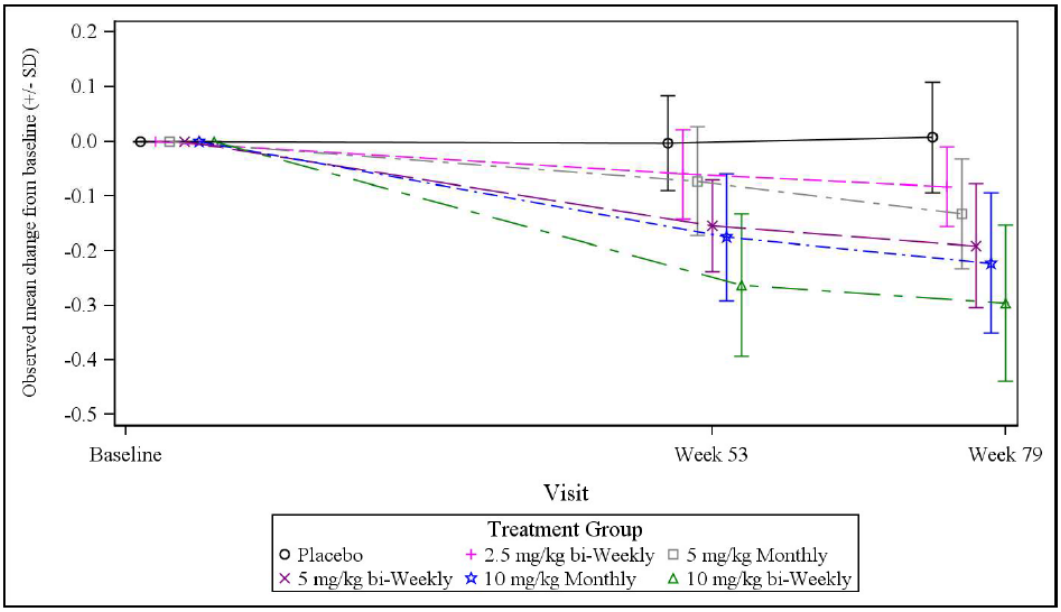


Figure 4 Observed Mean (SD) Change From Baseline in Brain Amyloid Levels as Measured by Amyloid PET SUVr Normalized to Whole Cerebellum Mask by Visit - Overall - PD Analysis Set 2

PD Analysis Set 2 is the group of subjects who had sufficient amyloid PET data to derive at least 1 amyloid PET parameter.
PD = pharmacodynamics, PET = positron emission tomography, SUVr = standard uptake value ratio.
Source: Figure 14.2.2.3.2e

Figure 9. Observed mean (SD) change from baseline in brain amyloid levels as measured by amyloid PET SUVr normalised to whole cerebellum mask by visit - overall - PD analysis set 2

- *Change from Baseline at 18 months in ADCOMS*

Table 12. Summary of MMRM analyses of change from baseline in ADCOMS at 18 months - full analysis set

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

Change from Baseline for each parameter in overall population was analyzed using MMRM with treatment group/combined treatment group, visit, disease stage (MCI due to AD, mild AD dementia), ApoE4 status (carrier, non-carrier), presence or absence of concomitant AD treatment (AChEIs and/or memantine) at Baseline, region, treatment group-by-visit interaction as factors, and Baseline value as covariate. The mixed-effects model within each randomization stratum (subgroup) was similar and was reduced by removing corresponding stratification factor from the model in overall population. Subjects were censored at the time of initiation or change of AChEIs or memantine treatment regimens.
AChEIs = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ApoE4 = apolipoprotein ϵ4 variant, LS = least square, MCI = mild cognitive impairment, MMRM = mixed-effects model with repeated measures.
Source: Table 14.2.1.5a and Table 14.2.1.5.1a

Table 13. Summary of MMRM analyses of change from baseline in ADCOMS at 18 months by ApoE4 status - full analysis set

Visit Strata Level Statistic	Placebo (N = 238)	BAN2401 2.5 mg/kg bi-Weekly (N = 52)	BAN2401 5 mg/kg Monthly (N = 48)	BAN2401 5 mg/kg bi-Weekly (N = 89)	BAN2401 10 mg/kg Monthly (N = 246)	BAN2401 10 mg/kg bi-Weekly (N = 152)
Week 79						
ApoE4 Positive						
n	113	24	26	55	129	10
Least Square Mean	0.202	0.167	0.192	0.189	0.161	0.075
SE	0.020	0.043	0.041	0.028	0.019	0.056
LS Mean Difference: Active Dose - Placebo		-0.035	-0.011	-0.013	-0.041	-0.127
90% Confidence Interval for Differences		-0.111, 0.041	-0.084, 0.063	-0.069, 0.042	-0.084, 0.002	-0.224, -0.030
p-value		0.450	0.813	0.693	0.117	0.031
ApoE4 Negative						
n	47	9	9	6	17	69
Least Square Mean	0.174	0.186	0.193	0.280	0.181	0.160
SE	0.030	0.063	0.068	0.082	0.047	0.025
LS Mean Difference: Active Dose - Placebo		0.012	0.019	0.106	0.008	-0.013
90% Confidence Interval for Differences		-0.101, 0.124	-0.102, 0.140	-0.036, 0.249	-0.082, 0.097	-0.074, 0.047
p-value		0.862	0.797	0.219	0.889	0.713

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

Table 14. Summary of MMRM analyses of change from baseline in CDR-SB at 18 months - full analysis set

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

The change from Baseline for each parameter in overall population was analyzed using the MMRM with treatment group/combined treatment groups, visit, disease stage (MCI due to AD, mild AD dementia), ApoE4 status (carrier, non-carrier), presence or absence of concomitant AD treatment (AChEIs and/or memantine) at Baseline, region, treatment group-by-visit interaction as factors, and Baseline value as covariate. The mixed-effects model within each randomization stratum (subgroup) was similar and was reduced by removing corresponding stratification factor from the model in overall population. Subjects were censored at the time of initiation or change of AChEIs or memantine treatment regimens.
AChEIs = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ApoE4 = apolipoprotein ϵ4 variant, CDR-SB = Clinical Dementia Rating-Sum of Boxes, LS = least square, MCI = mild cognitive impairment, MMRM = mixed-effects model with repeated measures.
Source: Table 14.2.1.5d and Table 14.2.1.5.1d

Table 15. Summary of MMRM analyses of change from baseline in CDR-SB at 18 months – full analysis set

Visit Strata Level Statistic	Placebo (N = 238)	BAN2401 2.5 mg/kg bi-Weekly (N = 52)	BAN2401 5 mg/kg Monthly (N = 48)	BAN2401 5 mg/kg bi-Weekly (N = 89)	BAN2401 10 mg/kg Monthly (N = 246)	BAN2401 10 mg/kg bi-Weekly (N = 152)
Week 79						
ApoE4 Positive						
n	114	24	27	61	132	10
Least Square Mean	1.645	1.205	1.689	1.393	1.245	0.660
SE	0.193	0.410	0.389	0.264	0.182	0.542
LS Mean Difference: Active Dose - Placebo		-0.439	0.044	-0.252	-0.399	-0.985
90% Confidence Interval for Differences		-1.171, 0.292	-0.657, 0.744	-0.775, 0.272	-0.812, 0.013	-1.921, -0.050
p-value		0.323	0.918	0.428	0.111	0.083
ApoE4 Negative						
n	47	10	9	6	17	74
Least Square Mean	1.130	1.122	1.644	2.015	1.166	1.207
SE	0.286	0.598	0.660	0.798	0.460	0.239
LS Mean Difference: Active Dose - Placebo		-0.008	0.515	0.885	0.037	0.077
90% Confidence Interval for Differences		-1.084, 1.068	-0.661, 1.690	-0.501, 2.271	-0.836, 0.909	-0.507, 0.661
p-value		0.990	0.470	0.292	0.945	0.827

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

Table 16. Summary of MMRM analyses of change from baseline in ADAS–Cog14 at 18 months – full analysis set

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

The change from Baseline for each parameter in overall population was analyzed using the MMRM with treatment group/combined treatment groups, visit, disease stage (MCI due to AD, mild AD dementia), ApoE4 status (carrier, non-carrier), presence or absence of concomitant AD treatment (AChEIs and/or memantine) at Baseline, region, treatment group-by-visit interaction as factors, and Baseline value as covariate. The mixed-effects model within each randomization stratum (subgroup) was similar and was reduced by removing corresponding stratification factor from the model in overall population. Subjects were censored at the time of initiation or change of AChEIs or memantine treatment regimens.
AChEIs = acetylcholinesterase inhibitor, AD = Alzheimer's disease, ApoE4 = apolipoprotein ϵ4 variant, ADAS–Cog14 = Alzheimer Disease Assessment Scale - Cognitive Subscale with 14 tasks, LS = least square, MCI = mild cognitive impairment, MMRM = mixed-effects model with repeated measures.
Source: Table 14.2.1.5b and Table 14.2.1.5.1b

Table 17. Summary of MMRM analyses of change from baseline in ADAS–Cog14 at 18 months by ApoE4 status – full analysis set

Visit Strata Level Statistic	Placebo (N = 238)	BAN2401 2.5 mg/kg bi-Weekly (N = 52)	BAN2401 5 mg/kg Monthly (N = 48)	BAN2401 5 mg/kg bi-Weekly (N = 89)	BAN2401 10 mg/kg Monthly (N = 246)	BAN2401 10 mg/kg bi-Weekly (N = 152)
Week 79						
ApoE4 Positive						
n	114	24	25	55	129	10
Least Square Mean	4.321	5.947	5.685	4.141	4.343	0.684
SE	0.698	1.446	1.402	0.952	0.659	1.891
LS Mean Difference: Active Dose - Placebo		1.626	1.364	-0.180	0.021	-3.637
90% Confidence Interval for Differences		-0.939, 4.192	-1.137, 3.865	-2.043, 1.683	-1.431, 1.474	-6.893, -0.381
p-value		0.297	0.369	0.873	0.981	0.066
ApoE4 Negative						
n	44	9	9	6	17	69
Least Square Mean	5.957	4.159	5.594	6.076	4.791	3.422
SE	1.259	2.624	2.842	3.427	1.970	1.069
LS Mean Difference: Active Dose - Placebo		-1.798	-0.363	0.119	-1.166	-2.535
90% Confidence Interval for Differences		-6.464, 2.869	-5.387, 4.661	-5.793, 6.032	-4.863, 2.532	-5.034, -0.036
p-value		0.525	0.905	0.973	0.603	0.095

2.6.5.2. Main study

BAN2401-G000-301

The MAA is based on a single confirmatory Phase 3 study: BAN2401-G000-301. This was an 18-month treatment, multicentre, double-blind, placebo-controlled, parallel-group study in subjects with Early Alzheimer Disease (EAD) (Mild Cognitive Impairment (MCI) due to AD or mild AD) with confirmed amyloid pathology indicated by positive amyloid load and designed to demonstrate the superiority of lecanemab versus placebo in subjects with EAD. Amyloid pathology was confirmed by amyloid PET assessment or cerebrospinal fluid (CSF) assessment of t-tau/Aβ.

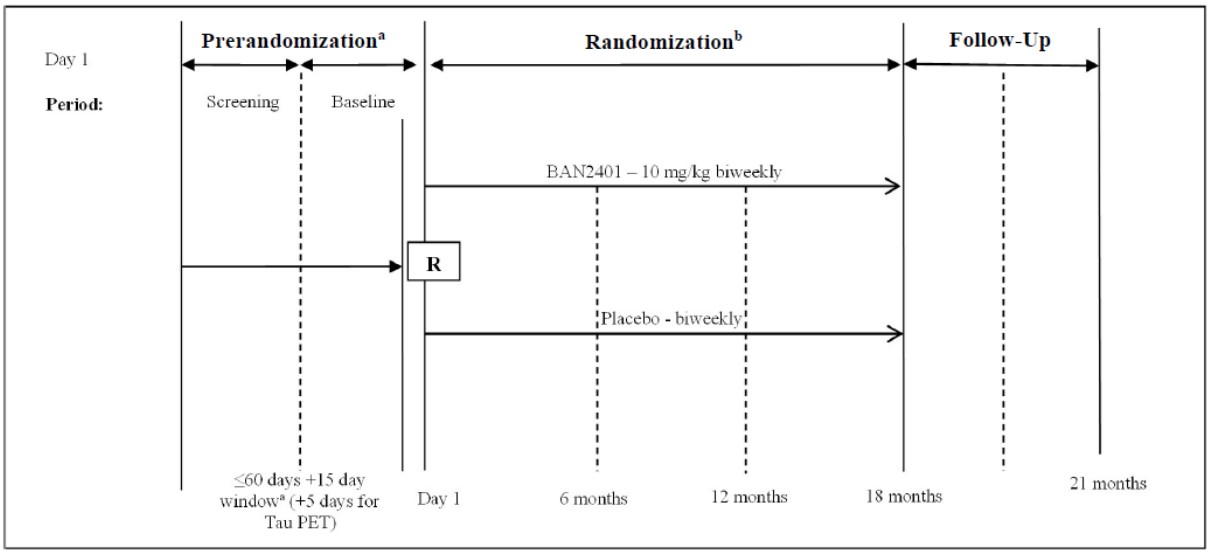


Figure 10. Study design of BAN2401-G000-301 – core study

Methods

Study Participants

The study population is adults with EAD (MCI due to AD with intermediate likelihood/prodromal AD or mild AD dementia) with confirmed amyloid pathology indicated by positive amyloid load (confirmed by amyloid PET assessment or CSF assessment of t-tau/Aβ).

Inclusion criteria

Main inclusion criteria are:

Diagnosis

MCI due to AD–intermediate likelihood:

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

Mild AD dementia:

4. Meet the NIA-AA core clinical criteria for probable AD dementia.
5. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline.

Key Inclusion Criteria that must be met by all subjects:

6. Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the WMS-IV LMII, as follows:

   a. ≤15 for age 50 to 64 years b. ≤12 for age 65 to 69 years c. ≤11 for age 70 to 74 years

   d. ≤9 for age 75 to 79 years e. ≤7 for age 80 to 90 years

7. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:

   a. PET assessment of imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.

   b. CSF assessment of t-tau/Aβ

8. Male or female subjects aged ≥50 and ≤90 years, at the time of informed consent.
9. MMSE score greater than or equal to 22 at Screening and Baseline and less than or equal to 30 at Screening and Baseline.
11. If receiving an approved AD treatment, such as AChEIs, or memantine, or both for AD, must be on a stable dose for at least 12 weeks prior to Baseline. Treatment-naïve subjects for AD medications can be entered into the study.
12. Have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject).

Exclusion criteria

Main exclusion criteria are:

3. Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD.
4. History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening.
5. Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the subject.
6. GDS score greater than or equal to 8 at Screening.
8. Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD.
9. Other significant pathological findings on brain MRI at Screening
10. Hypersensitivity to BAN2401 or any of the excipients, or to any monoclonal antibody treatment.
12. Subjects with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalised ratio [INR] >1.5 for subjects who are not on anticoagulant treatment, e.g., warfarin).
16. Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

Treatments

Active treatment

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

The dose has been selected based on the results of the Phase 2 BAN2401-G000-201 study (described above).

Control

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

Objectives

Primary objective

- The primary objective of this study was to evaluate the efficacy of lecanemab 10 mg/kg biweekly (LEC10-BW) in subjects with early Alzheimer's Disease (EAD) by determining the superiority of LEC10-BW compared with placebo on the change from baseline in the CDR-SB at 18 months of treatment.

Secondary objectives

- To determine whether LEC10-BW is superior to placebo in reducing brain amyloid levels as measured by amyloid PET using Centiloids at 18 months
- To evaluate the efficacy of LEC10-BW in subjects with EAD by determining the superiority of LEC10-BW compared with placebo on the change from baseline in the ADAS-Cog14 at 18 months of treatment
- To evaluate the efficacy of LEC10-BW in subjects with EAD by determining the superiority of LEC10-BW compared with placebo on the change from baseline in the ADCOMS at 18 months of treatment
- To evaluate the efficacy of LEC10-BW in subjects with EAD by determining the superiority of LEC10-BW compared with placebo on the change from baseline in the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 18 months of treatment
- To evaluate the safety and tolerability of LEC10-BW
- To evaluate the population PK of LEC10-BW

Outcomes/endpoints

Primary endpoint

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

Secondary endpoint

Key secondary endpoints

- Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels
- Change from baseline in ADAS-Cog14 at 18 months
- Change from baseline in ADCOMS at 18 months
- Change from baseline in ADCS MCI-ADL at 18 months

Other secondary endpoints

- Incidence of AEs and change in vital signs, ECGs, laboratory safety tests, suicidality assessments, and MRI safety parameters
- Population PK parameters of lecanemab in serum, including but not limited, to AUC and average concentration (Cav)

Sample size

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

Considering there were about 200 subjects who missed 3 or more consecutive doses due to COVID-19 pandemic, in agreement with FDA in Dec 2020, an additional approximately 200 subjects were randomised to retain 90% power, for a total sample size of approximately 1766 randomised subjects. To ensure that the study population is consistent with prior data used in the specified power calculations, approximately 70% of total number of subjects randomised were APOE4 carriers.

If there was an indication that sample size assumptions needed to be changed, a blinded sample size re-estimation was to be performed through estimated standard deviation based on blinded data before the completion of enrolment. This blinded sample size re-estimation was to be performed based on signals from external studies or based on review of blinded data from this study before the completion of enrolment. The standard deviation of the primary endpoint was estimated based on data from Study 201. It was possible that the standard deviation for the same endpoint in this study was larger than that due to study-to-study variation.

No comparative interim analysis was planned or conducted for this study.

Randomisation and blinding (masking)

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

Subjects were stratified according to clinical subgroup; use of AD symptomatic medication at baseline (yes or no), APOE4 carrier status (carriers or noncarriers) and geographical region.

Randomisation was performed centrally by an IxRS.

Randomisation was managed to ensure that approximately 70% of the total number of subjects randomised would be apolipoprotein E4 (APOE4) carriers. Additionally, no less than 50% of subjects were to be in the MCI due to AD clinical subgroup.

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

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

Statistical methods

Analysis populations

The ITT Full Analysis Set (FAS+) was the group of randomised subjects who received at least 1 dose of study drug, and who had a baseline assessment and at least one post dose primary efficacy measurement. This is the primary analysis population for EMA and PMDA.

Hypothesis testing and multiplicity adjustment

The primary null hypothesis was that there was no difference in the mean change from baseline in CDR-SB at 18 months between lecanemab and placebo groups. The null hypothesis was tested at a significance level of two-sided alpha =0.05.

If the primary endpoint was statistically significant, then the key secondary endpoints were to be tested in the following order: (1) change from baseline in amyloid PET using Centiloids at 18 months, (2) change from baseline in ADAS-Cog14 at 18 months, (3) change from baseline in ADCOMS at 18 months, and (4) change from baseline in ADCS MCI-ADL at 18 months. Each test was to be performed at a significance level of two-sided alpha=0.05 and only to be performed if the preceding test was statistically significant.

Primary analysis and Estimand

The primary analysis was performed on the ITT FAS+ for EMA.

The estimand (ICH E9 [R1], 2019) of the primary analysis was the mean difference of the change from baseline in CDR-SB at 18 months between treatment groups, regardless of intercurrent events such as initiation of new AD concomitant treatment or change of AD concomitant treatment or treatment discontinuation. In other terms, the treatment policy strategy was applied to these events. All observed data were included in the primary analysis, including data collected after the intercurrent events.

The primary analysis of the change from baseline in CDR-SB at 18 months were performed to compare lecanemab and placebo groups using a mixed-effects model with repeated measures (MMRM). The MMRM included baseline CDR-SB as a covariate, with treatment group, visit, stratification variables (i.e., clinical subgroup, use of AD symptomatic medication at baseline [yes, no], APOE4 carrier status (carriers, noncarriers), and geographical region [North America, Europe, and Asia Pacific]), baseline CDR-SB-by-visit, and treatment group-by-visit interaction as fixed effects. For stratification variables, actual data (laboratory data for APOE4 carrier status, CRF data for clinical subgroup and use of AD symptomatic medication at baseline, and IxRS data for geographical region) were used. An unstructured covariance matrix was employed to model the covariance of within-subject effect; if MMRM failed to converge then a covariance structure with fewer parameters were employed according to a pre-specified order in the list until the MMRM converges.

This primary analysis included all observed post baseline data of the change from baseline CDR-SB without imputation of missing values. The treatment effect for lecanemab and placebo was compared at 18 months based on the MMRM. The adjusted means, adjusted mean treatment difference and corresponding 95% CI were presented.

Given that not all patients were followed up after discontinuation, this method without compliance indicator is not considered conservative. This aspect is discussed below.

Sensitivity analyses

The sensitivity analysis using log-transformed change from baseline in CDR-SB was performed using an MMRM to correct for possible skewness of data. The MMRM included log-transformed baseline CDR-SB as a covariate, with treatment group, visit, randomisation stratification variables (i.e., clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, and geographical region), log-transformed baseline CDR-SB-by-visit, and treatment group-by-visit interaction as fixed effects.

The following sensitivity analyses were conducted to assess the robustness of the primary analysis to missing data:

- The sensitivity analysis using rank ANCOVA after multiple imputations (MIs) at 18 months was performed. The imputation model was a regression model including the following variables: baseline and post baseline observed values, treatment group, and stratification variables (i.e., clinical subgroup, AD symptomatic medication at baseline, APOE4 carrier status, and geographical region). Missing data was imputed via the imputation model using the standard MI method assuming missing at random (MAR) (Rubin, 1987). After 1000 imputations with pre-specified random seed, rank ANCOVA was performed using imputed datasets. The rank ANCOVA model included baseline CDR-SB as a covariate, with treatment group and randomisation stratification variables (i.e., clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, and geographical region) as factors. Analysis results from the imputed datasets were then combined based on Rubin's rules (Rubin, 1987). The Hodges-Lehmann estimate of median difference and its 95% CI was also calculated using imputed datasets and combined based on Rubin's rules (Rubin, 1987).
- Tipping point analysis using shift parameter (delta) separately for each treatment group based on MIs were performed. The missing data were first imputed by the imputation model specified from the rank ANCOVA after MIs approach (assuming MAR). To reflect the worse performance after early withdrawal, pre-specified shift parameters δ_c and δ_t were added to the imputed values for subjects on PBO and LEC10-BW, respectively. The adjusted multiple imputed datasets were then analysed by a rank ANCOVA model, and the results were combined using the Rubin's rule for inference. The P value was provided for each pair of shift parameters (δ_c, δ_t). The robustness of the primary analysis outcomes was evaluated based on the scientific plausibility of the tipping point.
- The analysis using the same model as the primary analysis with just one change which was using randomisation stratification variables based on IxRS classification (instead of actual data) was conducted.

Several additional sensitivity analyses were also performed:

- Repeated primary MMRM analyses censoring data after ARIA event – per FDA request
- Repeated primary analyses using pure ITT subjects (subjects randomised and received at least one dose of medication) – per EMA request
- Analyses attributing worst-case and worst 20% case values to patients whose missingness follows the occurrence of ARIA and analyses with time-varying discontinuation indicators – per EMA request

<u>Key secondary analyses</u>

Key secondary analyses were performed on the ITT FAS+ for EMA and PMDA

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

Amyloid PET SUVR composite is a simple average of the SUVR in the following brain regions: posterior cingulum (left and right), parietal cortex (left and right), lateral temporal cortex (left and right), and frontal cortex (left and right). Whole cerebellum was used as reference region. Amyloid PET using Centiloids was derived from this composite SUVR.

- Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels was analysed using the following in the model instead of baseline CDR-SB and baseline CDR-SB-by-visit interaction:
- The same MMRM as CDR-SB to compare LEC10-BW compared to PBO on the PD Analysis Set

- Baseline amyloid PET using Centiloids
- Baseline amyloid PET using Centiloids-by-visit interaction

Change from baseline in ADAS-Cog14, ADCOMS, ADCS MCI-ADL at 18 months

Change from baseline in ADAS-Cog14, ADCOMS, ADCS MCI-ADL at 18 months was analysed using same MMRM as CDR-SB to compare lecanemab and placebo, using baseline ADAS-Cog14 and baseline ADAS-Cog14-by-visit interaction in the model instead of baseline CDR-SB and baseline CDR-SB-by-visit interaction. Additional sensitivity analysis for this endpoint was performed as appropriate.

The following supplementary analyses were conducted using the same approach:

- Analysis on the PP Analysis Set
- Analysis censoring data after treatment discontinuation or initiation or dose adjustment of AD treatment regimens

Subgroup analyses

The primary endpoint, key secondary endpoints, and secondary endpoints related to clinical assessments will be analysed to evaluate the following subgroups; age group (<65 years, ≥65 years, ≥65 to <75 years, ≥75 years), sex, ethnicity (Hispanic-Latino, Not Hispanic-Latino), race (White, Black or African American, Asian, Other), geographical region, clinical subgroup (MCI due to AD, Mild AD Dementia), APOE4 carrier status (carriers or noncarriers), APOE4 genotype (homozygous carriers, heterozygous carriers, or noncarriers), use of AD symptomatic medication at baseline (yes or no). Subgroup by stratification variables (i.e., clinical subgroup, use of AD symptomatic medication at baseline, APOE4 carrier status, and geographical region) will be summarised using actual data (laboratory data for APOE4 carrier status, CRF data for clinical subgroup and use of AD symptomatic medication at baseline, IxRS data for geographical region).

Changes in planned analyses

There were 10 amendments to the original study protocol. The table below lists some of these modifications with an impact on the planned study methodology and analyses.

Protocol amendment	Changes
Amendment 1 (v2.0. 05 Apr 2019)	Addition of sample size re-estimation due to possibility of standard deviation variation between the present study and Study BAN2401-G000-201 (Study 201)
Amendment 6 (v7.0, 19 Jun 2020)	Clarification that that the study will enrol no less than 70% APOE4 carriers
Amendment 7 (v8.0, 21 Dec 2021)	Increased sample size to offset data loss from subjects who missed 3 or more consecutive doses during the COVID 19 pandemic
Amendment 8 (v10.0, 24 Feb 2022)	Addition of modified iADRS as other secondary endpoint and other secondary objective to evaluate disease progression using integrated measurement tool The evaluation of efficacy using the ADCOMS was changed from a key secondary to other secondary objective to specify analysis strategy for assessing LEC10-BW treatment effects

	The evaluation of quality of life using the ADCS MCI-ADL was changed from an exploratory to a key secondary objective to specify analysis strategy for assessing LEC10-BW treatment effects Described second database lock for subjects from China; clarification of timing of final database lock Revised the definition of the Full Analysis Set and defined a Full Analysis Set – Plus group to account for missed dosing during COVID-19 shutdown of the study sites
Amendment 9 (v11.0, 08 Jun 2022)	Region-specific changes to the key secondary and other secondary objectives and endpoints to the Core Study, and addition of exploratory objectives and endpoints to the Core Study to reflect feedback received from FDA and EMA regulatory authorities
Amendment 10 (v12.0, 24 Aug 2022)	Clarification of analyses for regulatory authorities

The database was locked on 13 September 2022. There were two versions of the statistical analysis plan (SAP). The original SAP (v1.0) was finalised on 9 April 2019. The revised SAP (v2.0) was finalised on 6 September 2022, with changes implemented to align with protocol amendments and to handle and assess deviations due to the COVID-19 pandemic.

A SAP addendum was also created on 20 October 2022 to address changes in immunogenicity analyses, based on feedback from the FDA.

Results

Participant flow

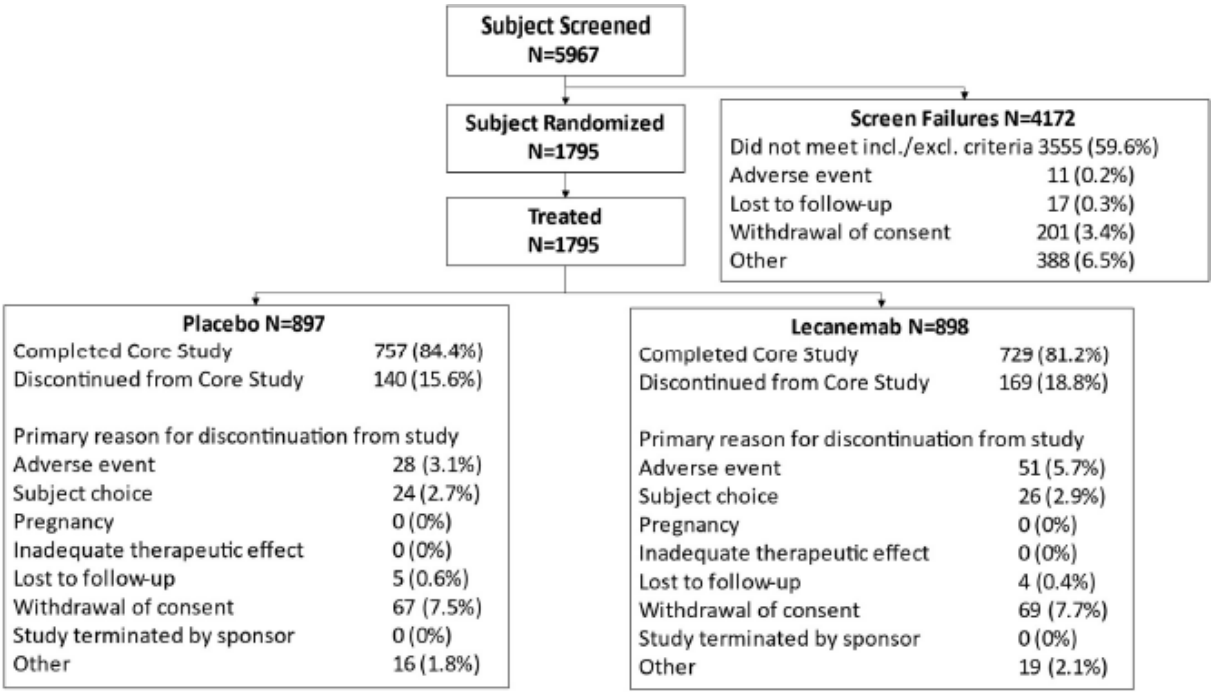


Figure 11. Disposition for BAN2401-G000-301 – core study

Recruitment

BAN2401-G000-301 was conducted between 27 Mar 2019 and 25 Aug 2022 at 235 study sites that randomised subjects in North America (112), Europe (which includes Australia, 55), Asia-Pacific (47), and China (21).

Conduct of the study

There were 10 amendments to the original study protocol (v1.0, 29 Jan 2019). Details of important changes made in each protocol amendment are given below.

Amendment 8 (v10.0, 24 Feb 2022) included, among others, the following major changes to the study protocol:

- The evaluation of efficacy using the ADCOMS was changed from a key secondary to other secondary objective to specify analysis strategy for assessing LEC10-BW treatment effects
- The evaluation of quality of life using the ADCS MCI-ADL was changed from an exploratory to a key secondary objective to specify analysis strategy for assessing LEC10-BW treatment effects

Baseline data

Demographic and other baseline characteristics of the randomised subjects are presented in below tables.

Table 18. Demography and baseline characteristics – core study (safety analysis set)

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

Percentages are based on the total number of subjects in relevant treatment group.
AD = Alzheimer's disease, APOE4 = apolipoprotein E4, CRF = case report form, IxRS = interactive voice and web response system, MCI = mild cognitive impairment, Min = minimum, Max = maximum.
a: Age is calculated at Date of Informed Consent.
Source: Table 14.1.4.1.3.

Numbers analysed

A summary of the number (percentage) of subjects in each analysis set is presented in Table 19.

Table 19. Demography analysis sets (randomised set) – core study

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

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

Table 20. Summary of important protocol deviations – core study (randomised set)

	Placebo (N = 897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)	Combined Total (N = 1795) n (%)
Subjects with any important protocol deviations	95 (10.6)	102 (11.4)	197 (11.0)
Assessments performed in incorrect order	0	1 (0.1)	1 (0.1)
Assessments performed out of window	0	1 (0.1)	1 (0.1)
CDR rater unblinded to subjects safety MRI or AE data	0	2 (0.2)	2 (0.1)
Exclusion criteria	7 (0.8)	3 (0.3)	10 (0.6)
Inclusion criteria	1 (0.1)	1 (0.1)	2 (0.1)
Incorrect Treatment	2 (0.2)	10 (1.1)	12 (0.7)
Incorrect dose	0	1 (0.1)	1 (0.1)
Infusion instructions not followed	3 (0.3)	2 (0.2)	5 (0.3)
Lack of sub-study consent	7 (0.8)	6 (0.7)	13 (0.7)
Longitudinal PET scan / lumbar puncture performed without valid baseline assessment OR using different tracer compared to baseline	1 (0.1)	3 (0.3)	4 (0.2)
Missed efficacy/PD/PK assessment(s) during treatment period	7 (0.8)	11 (1.2)	18 (1.0)
Missed safety assessment during treatment period	5 (0.6)	7 (0.8)	12 (0.7)
SAE/AE reporting	0	4 (0.4)	4 (0.2)
Whole visit(s) missing - 4 or more consecutive visits	60 (6.7)	53 (5.9)	113 (6.3)
Whole visit(s) missing - up to 3 consecutive visits	4 (0.4)	6 (0.7)	10 (0.6)

Outcomes and estimation

Primary endpoint

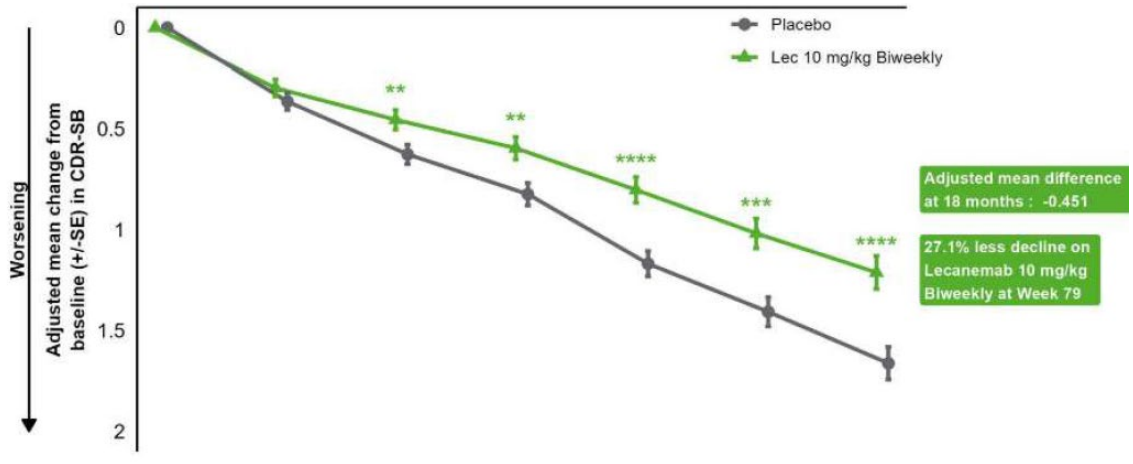
Change from baseline in CDR-SB at 18 months

The primary analysis was the adjusted mean difference of the change from baseline in CDR-SB at 18 months between PBO and LEC10-BW on ITT FAS+ (Table 21). The study met its pre-specified endpoint.

Table 21. Change from baseline in CDR-SB score at 18 months – MMRM – core study – intent to treat (full analysis set+)

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

m shows the number of subjects who are included in MMRM, n shows the number of subjects at each visit. The change from baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. Missing values are not imputed and assumed to be missing at random. % difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
AD = Alzheimer's disease, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, m = number of subjects included in the MMRM, MMRM = mixed model for repeated measures, N = number of subjects in treatment group.
Source: Table 14.2.1.1.2.



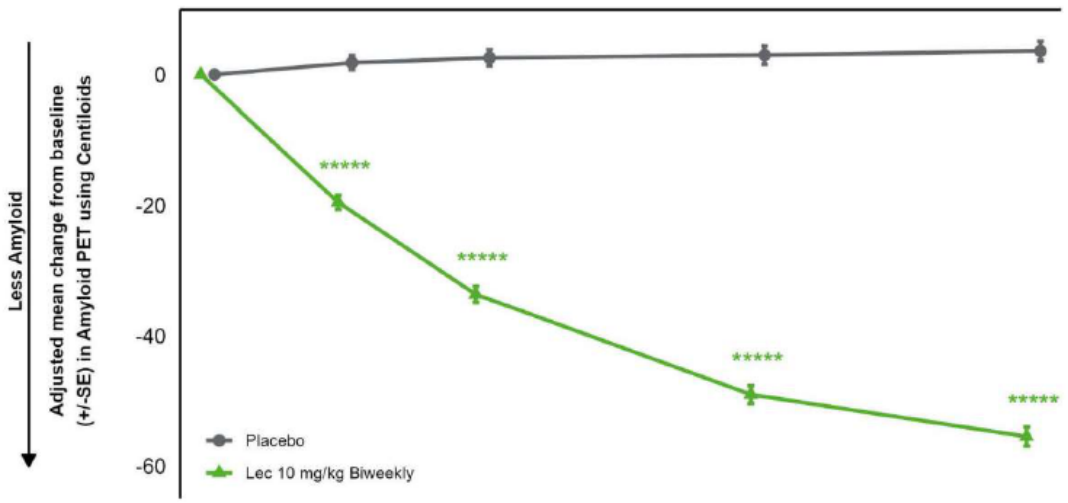
	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

Figure 12. Plot of adjusted mean change (±SE) from baseline in CDR-SB – core study – intent to treat (full analysis set+)

Secondary endpoints

Change from baseline in amyloid pet using centiloids at 18 months for brain amyloid levels

In this clinical study, the baseline level was 77.9 Centiloids, and at the end of the study, the level was 23.0 in LEC10-BW.



	Baseline	Week 13	Week 27	Week 53	Week 79
Placebo	344	303	286	259	205
Lec 10 mg/kg Biweekly	354	296	275	276	210

Figure 13. Plot of adjusted mean (±SE) of change from baseline in amyloid PET using Centiloids for brain amyloid levels – core study (PD analysis set)

Change from baseline of ADAS-Cog14 at 18 months

Change in ADAS-Cog14 is presented below.

Table 22. Summary of change from baseline in ADAS-Cog14 at 18 months – core study intent to treat (full analysis set+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADAS-Cog14		
Week 79		
n	740	705
Mean (SD)	28.55 (11.873)	28.00 (10.858)
Median	28.00	28.00
Min, Max	1.3, 90.0	2.0, 86.0
Change from Baseline		
n	738	703
Mean (SD)	4.61 (8.305)	3.80 (7.783)
Median	3.66	3.33
Min, Max	-14.0, 47.3	-25.7, 40.0

Table 23. Change from baseline in ADAS-Cog14 at 18 months – MMRM core study intent to treat (full analysis set+)

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

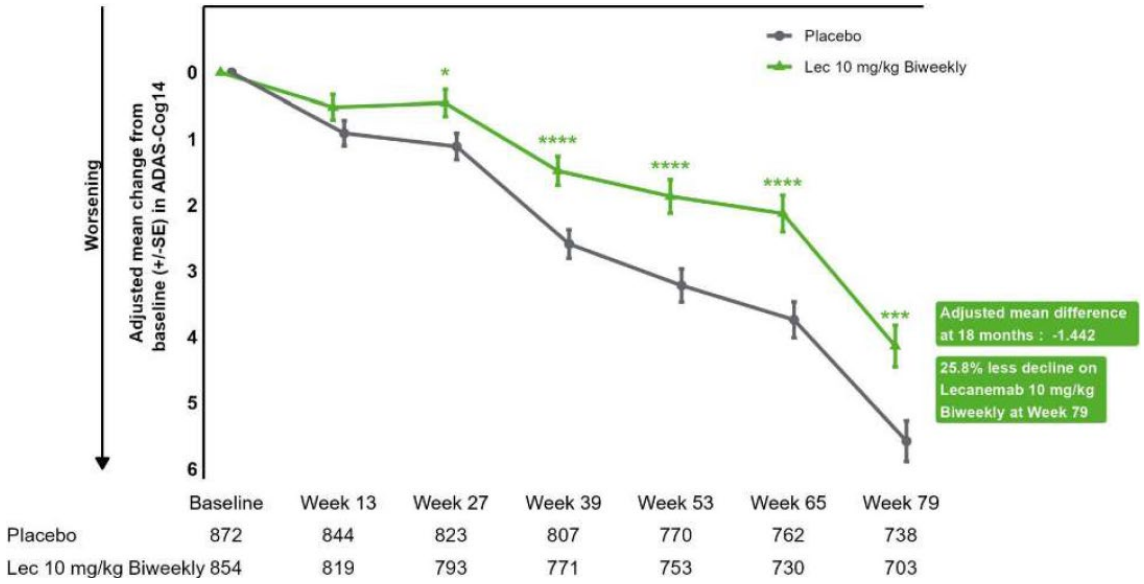


Figure 14. Change from baseline in ADAS-Cog14 – core study – intent to treat (full analysis set+)

Change from baseline of ADCOMS at 18 months

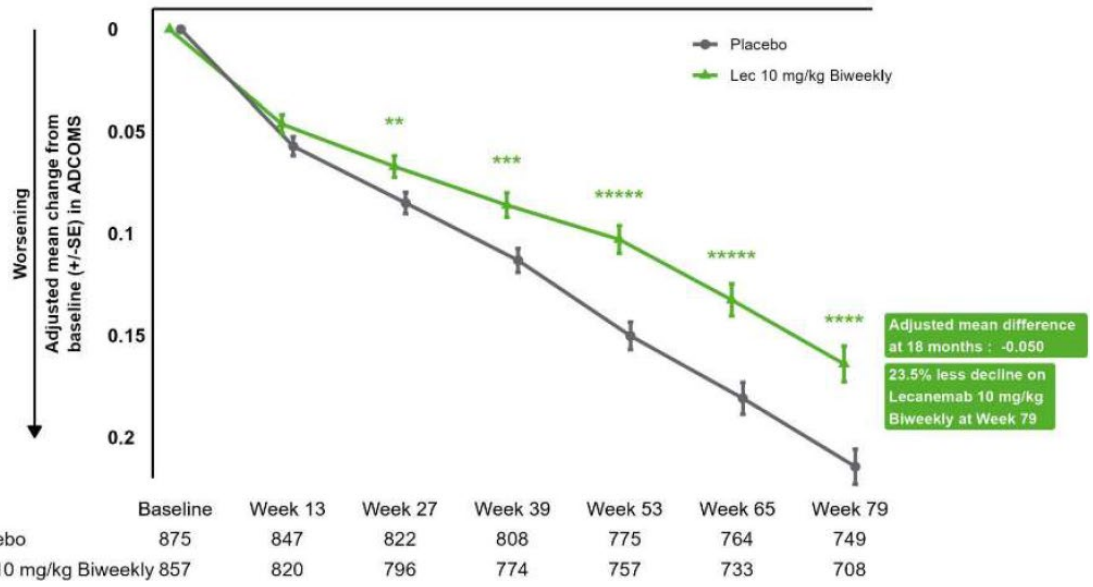
Change in ADCOMS is presented below.

Table 24. Summary of change from baseline in ADCOMS at 18 months – core study intent to treat (full analysis set+)

Parameter Visit Statistic	Placebo (N = 875)	Lecanemab 10 mg/kg Biweekly (N = 859)
ADCOMS		
Week 79		
n	749	708
Mean (SD)	0.583 (0.3036)	0.541 (0.2784)
Median	0.530	0.485
Min, Max	0.00, 1.92	0.05, 1.57
Change from Baseline		
n	749	708
Mean (SD)	0.193 (0.2463)	0.152 (0.2213)
Median	0.144	0.110
Min, Max	-0.32, 1.39	-0.24, 1.18

Table 25. Change from baseline in ADCOMS at 18 months – MMRM core study intent to treat (full analysis set+)

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



	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	847	822	808	775	764	749
Lec 10 mg/kg Biweekly	857	820	796	774	757	733	708

Figure 15. Change from baseline in ADCOMS – core study intent to treat (full analysis set+)

Change from baseline of ADCS MCI-ADL at 18 months

Change in ADCS MCI-ADL are presented below.

Table 26. Summary of change from baseline in ADCS MCI-ADL at 18 months – core study intent to treat (full analysis set+)

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

Table 27. Change from baseline in ADCS MCI-ADL at 18 months – MMRM core study intent to treat (full analysis set+)

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

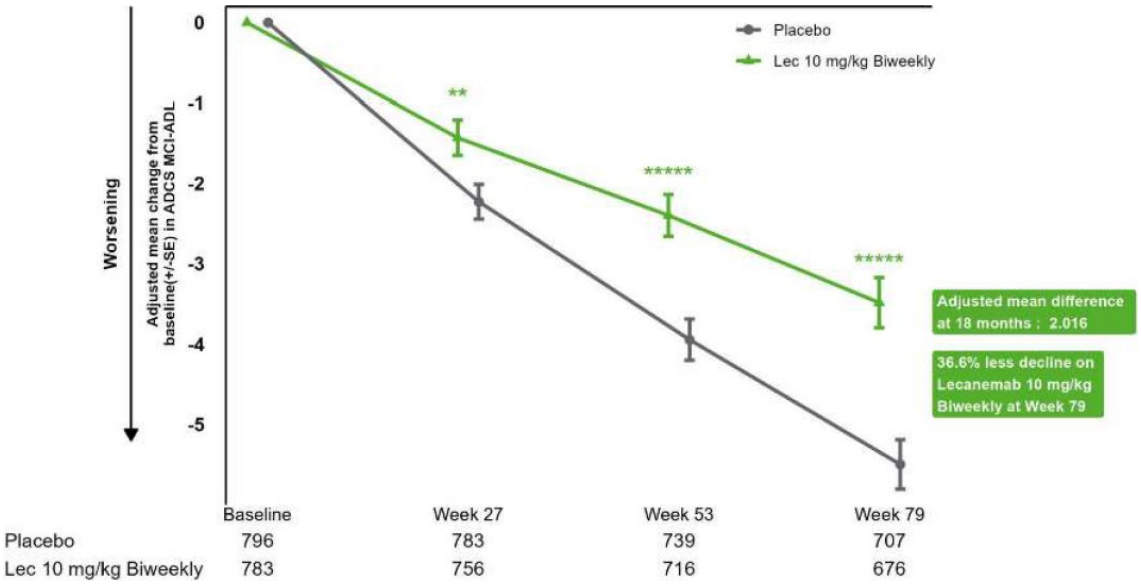


Figure 16. Change from baseline in ADCS MCI-ADL – core study intent to treat (full analysis set+)

Ancillary analyses

Subgroup analysis

CDR-SB

Results are displayed by randomisation strata.

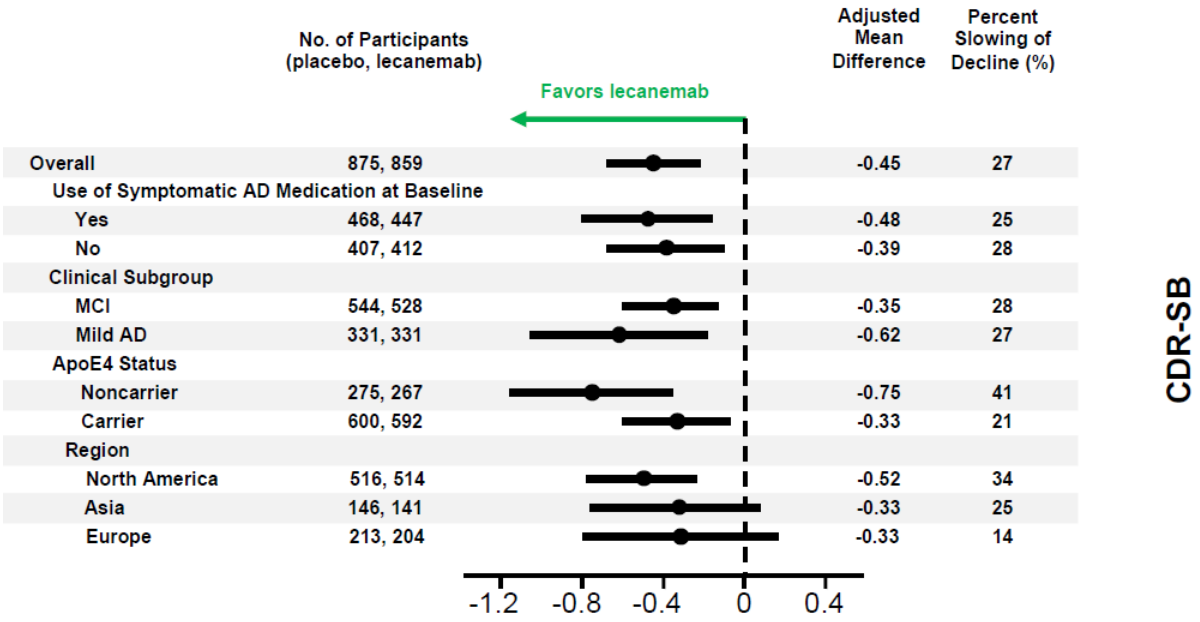


Figure 17. Adjusted mean difference in CDR-SB versus placebo (95% CI) - lecanemab versus placebo by randomisation strata – core study – intent to treat (full analysis set+)

Results are displayed by intrinsic factors.

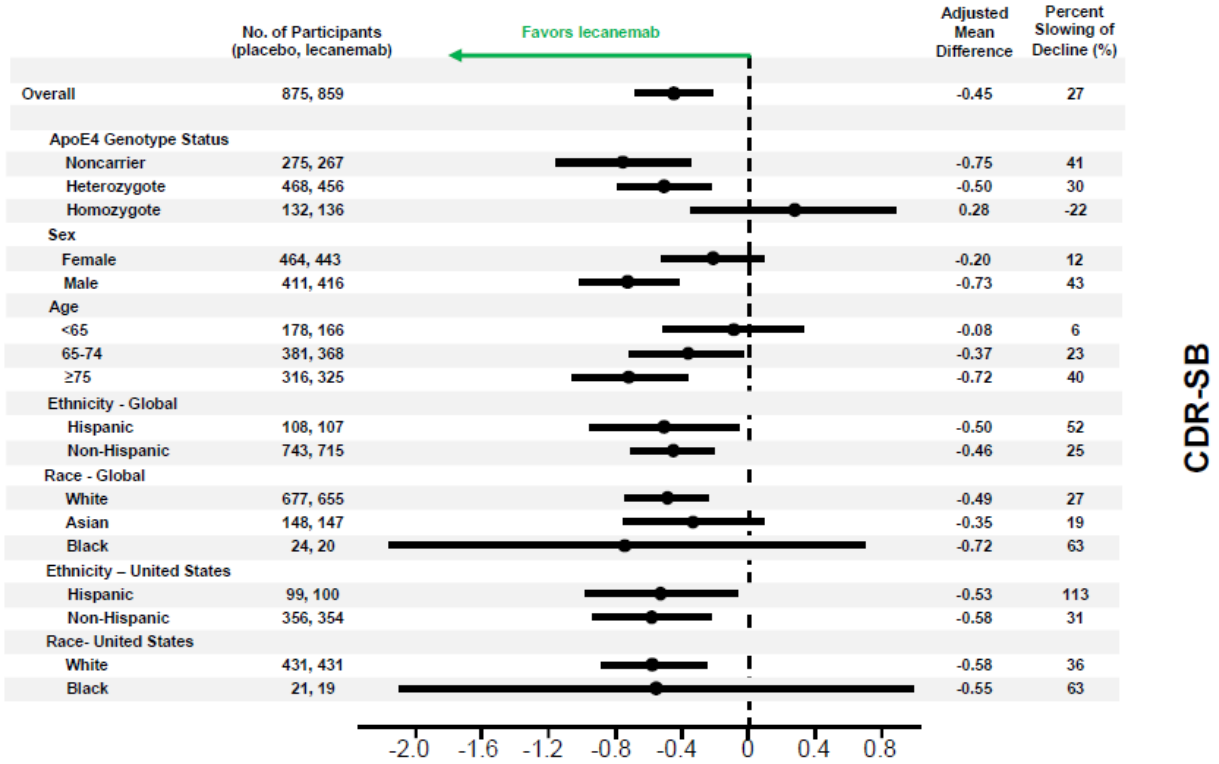


Figure 18. Adjusted mean difference in CDR-SB versus placebo (95% CI) - lecanemab versus placebo by intrinsic factors – core study – intent to treat (full analysis set+)

Amyloid PET

Results are displayed by clinical subgroup and APOE4 Carrier Status.

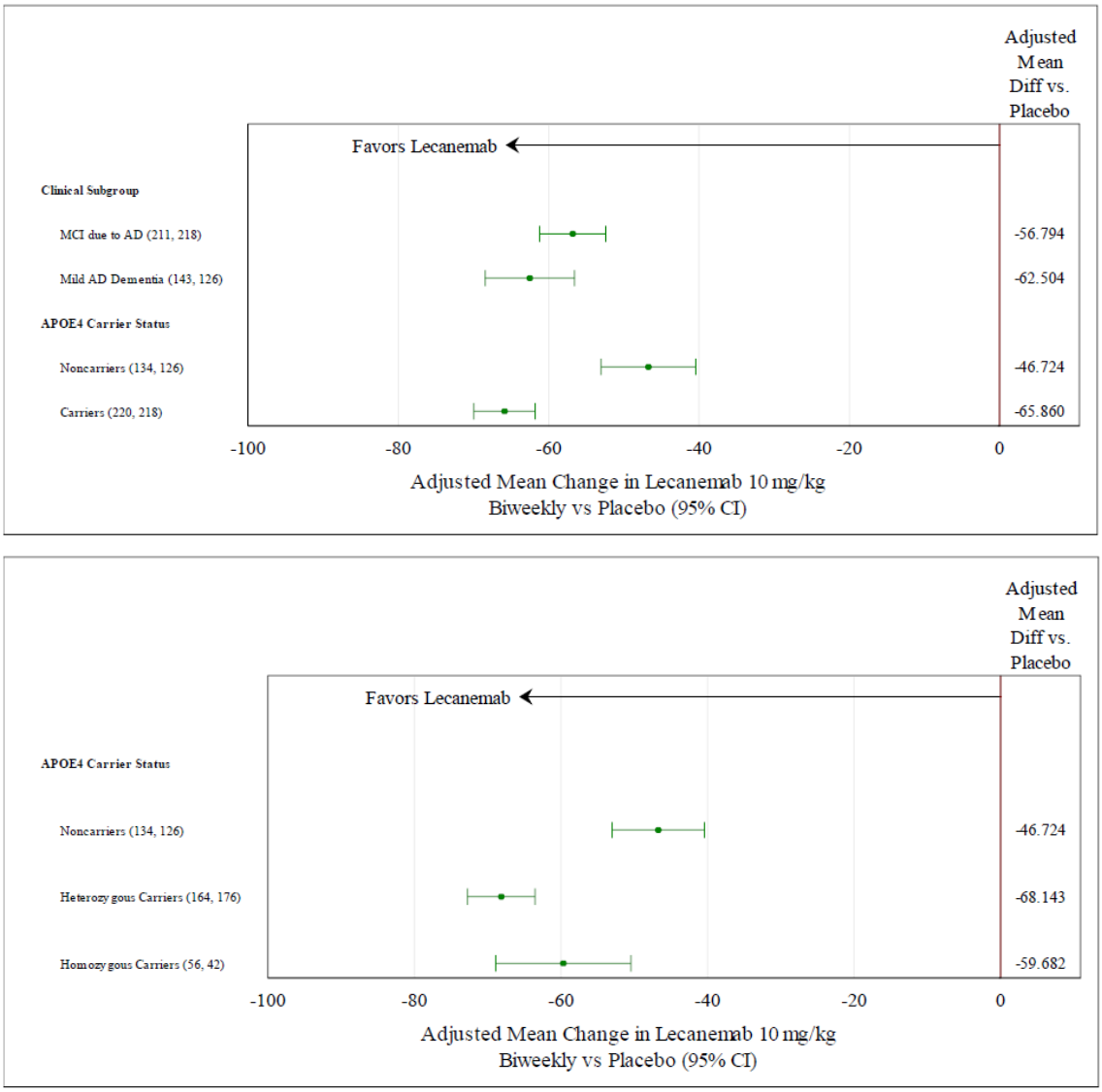


Figure 19. Forest plot of change from baseline in amyloid PET using centiloids at 18 months core study PD analysis set (amyloid PET) by clinical subgroup and APOE4 carrier status – core study – PD analysis set (amyloid PET)

Correlation

Correlations for change from baseline between amyloid PET using centiloids and clinical efficacy measures

Correlation with CDR-SB is presented below.

Table 28. Correlation analysis for change from baseline in amyloid PET using centiloids at week 79 and change from baseline in CDR-SB at week 79 – intent to treat (full analysis set+) and PD analysis set (amyloid PET)

Pairs Statistic	Placebo (N = 351)	Lecanemab 10 mg/kg Biweekly (N = 362)	Combined Total (N = 713)
Change from baseline in amyloid PET using Centiloids at Week 79 and change from baseline in CDR-SB at Week 79			
n	204	203	407
Pearson correlation	-0.053	-0.165	-0.016
P-value	0.44811	0.01901	0.75461
Spearman correlation	0.005	-0.277	-0.042
P-value	0.94728	0.00006	0.39509
Partial Pearson correlation	-0.013	0.114	0.120
P-value	0.84921	0.10618	0.01540
Partial Spearman correlation	0.045	0.082	0.095
P-value	0.52307	0.24489	0.05538

See the Clinical sections below for the correlation with the key clinical endpoints.

Concomitant medication

The proportion of subjects who have received a concomitant AD symptomatic medication during the study is presented below.

Table 29. Concomitant Alzheimer's disease medications – core study (safety analysis set)

Anatomical Class Therapeutic Subclass Pharmacological Subclass WHO Drug Name(Preferred Term)	Placebo (N = 897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)	Combined Total (N = 1795) n (%)
Subjects who took at least one medication	519 (57.9)	514 (57.2)	1033 (57.5)
Nervous system	519 (57.9)	514 (57.2)	1033 (57.5)
Psychoanaleptics	519 (57.9)	514 (57.2)	1033 (57.5)
Anti-dementia drugs	519 (57.9)	514 (57.2)	1033 (57.5)
Donepezil	361 (40.2)	361 (40.2)	722 (40.2)
Donepezil;memantine	6 (0.7)	5 (0.6)	11 (0.6)
Galantamine	33 (3.7)	40 (4.5)	73 (4.1)
Memantine	127 (14.2)	120 (13.4)	247 (13.8)
Rivastigmine	86 (9.6)	66 (7.3)	152 (8.5)

The concomitant medication status thorough of the subject who were on symptomatic AD medication at baseline is presented below.

Table 30. Subject's status on Alzheimer's disease medications - core study (safety analysis set)

Category	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)	Combined Total (N=1795) n (%)
Subjects on AD medication at baseline	477 (53.2)	466 (51.9)	943 (52.5)
Subjects who remained on stable dose	421 (46.9)	419 (46.7)	840 (46.8)
Subjects who did not remain on stable dose	56 (6.2)	47 (5.2)	103 (5.7)
Subjects who started new medication	22 (2.5)	15 (1.7)	37 (2.1)
Subjects who changed dose of existing medication	38 (4.2)	32 (3.6)	70 (3.9)
Subjects who increased dose of existing medication	31 (3.5)	26 (2.9)	57 (3.2)
Subjects who decreased dose of existing medication	18 (2.0)	13 (1.4)	31 (1.7)
Subjects who stopped the existing medication	24 (2.7)	19 (2.1)	43 (2.4)
Subjects not on AD medication at baseline	420 (46.8)	432 (48.1)	852 (47.5)
Subjects who started new medication	45 (5.0)	49 (5.5)	94 (5.2)
Subjects who started new AD medication regardless of use at baseline	67 (7.5)	64 (7.1)	131 (7.3)

Post-hoc analysis

Post-hoc analysis were conducted for answering questions.

Sensitivity analysis

Additional sensitivity analyses were conducted in answers to questions. The below tables show the results of primary and key secondary endpoints based on the combination of imputation rules.

Table 31. Sensitivity analyses using worst case, worst 20% case, and best 20% case imputation for missing due to discontinuation by ARIA and copy-increments from reference imputation for others – study 301 core (randomised set)

Endpoint	Case	Difference	% less decline	*P* value
CDR-SB	Worst	-0.249	14.7%	0.04827
	Worst 20%	-0.428	25.4%	0.00017
	Best 20%	-0.470	27.9%	0.00003
	Main analysis	-0.451	27.1%	0.00005
ADAS-Cog14	Worst	-0.689	12.2%	0.15471
	Worst 20%	-1.323	23.6%	0.00277
	Best 20%	-1.507	26.9%	0.00065
	Main analysis	-1.442	25.8%	0.00065
ADCS MCI-ADL	Worst	1.158	20.9%	0.00934
	Worst 20%	1.601	29.0%	0.00012
	Best 20%	1.758	31.9%	0.00002
	Main analysis	2.016	36.6%	<0.00001

ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14 item version, ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, CDR-SB = Clinical Dementia Rating-Sum of Boxes.
Source: Appendix 1 Tables 14.2.1.2.34, 14.2.1.2.35, 14.2.1.2.39, 14.2.2.2.23, 14.2.2.2.24, 14.2.2.2.28, 14.2.2.4.23, 14.2.2.4.24, 14.2.2.4.28.

Responder analysis

Analysis showing results on the proportion of patients showing CDR-SB worsening value corresponding to certain "thresholds" – or more - at 18 months were provided during the assessment procedure.

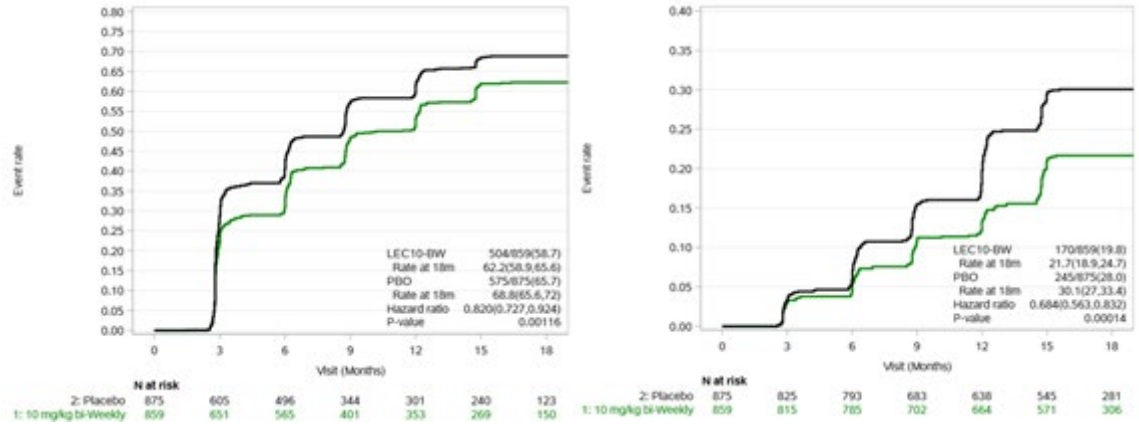


Figure 20. Time to worsening of CDR-SB by MCID cutoff 0.5 (left) and 2.0 (right) – study 301 ITT FAS+

2.6.5.1. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of efficacy for trial BAN2401-G000-301

Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease			
Study identifier	BAN2401-G000-301		
Design	Study 301 was a global, multicentre, double-blind, PBO controlled, parallel group study to demonstrate the superiority of LEC10-BW compared to PBO. Study 301 Core was an 18-month study in which eligible subjects were randomised in a 1:1 ratio to receive either LEC10-BW or PBO biweekly.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		21 months Not applicable Up to 2 years, or until commercial availability of lecanemab, or until a positive risk-benefit assessment in this indication is not demonstrated.
Hypothesis	Superiority		
Treatments groups	lecanemab		lecanemab 10 mg/kg biweekly, 18 months, 898
	Placebo		0.9% sodium chloride biweekly, 18 months, 897
Endpoints and definitions	Primary endpoint	CDR-SB	Change from baseline in the CDR-SB at 18 months
	Key secondary endpoint	Amyloid PET	Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels

Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease				
Study identifier	BAN2401-G000-301			
	Key secondary endpoint	ADAS-Cog14	Change from baseline in ADAS-Cog14 at 18 months	
	Key secondary endpoint	ADCOMS	Change from baseline in ADCOMS at 18 months	
	Key secondary endpoint	ADCS MCI-ADL	Change from baseline in ADCS MCI-ADL at 18 months	
Database lock	13 Sep 2022			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 18 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Lecanemab	
	Number of subjects	N=875	N=859	
	CDR-SB Adjusted mean	1.663	1.213	
	(SE)	(0.080)	(0.082)	
	Amyloid PET Adjusted mean	3.637	-55.481	
	(SE)	(1.470)	(1.457)	
	ADAS-Cog14 Adjusted mean	5.581	4.140	
	(SE)	(0.309)	(0.314)	
	ADCOMS Adjusted mean	0.214	0.164	
	(SE)	(0.009)	(0.009)	
	ADCS MCI-ADL Adjusted mean	-5.500	-3.484	
	(SE)	(0.308)	(0.313)	

Effect estimate per comparison	CDR-SB	Comparison groups	Lecanemab - Placebo
		Adjusted mean difference:	-0.451
		95% CI	(-0.669, -0.233)
		P-value	0.00005
	Amyloid PET	Comparison groups	Lecanemab - Placebo
		Adjusted mean difference:	-59.118
		95% CI	-62.640, -55.596
		P-value	<.00001
	ADAS-Cog14	Comparison groups	Lecanemab - Placebo
		Adjusted mean difference:	-1.442
		95% CI	-2.270, -0.613
		P-value	0.00065
	ADCOMS	Comparison groups	Lecanemab - Placebo
		Adjusted mean difference:	-0.050
		95% CI	-0.074, -0.027
		P-value	0.00002
	ADCS MCI-ADL	Comparison groups	Lecanemab - Placebo
		Adjusted mean difference:	2.016

Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study With an Open-Label Extension Phase to Confirm Safety and Efficacy of BAN2401 in Subjects With Early Alzheimer's Disease			
Study identifier	BAN2401-G000-301		
		95% CI	1.208, 2.823
		P-value	<.00001
Analysis description	**Primary Analysis and Key Secondary Analysis:** Pre-specified analysis Testing hierarchy strategy		

2.6.5.2. Supportive study(ies)

The development programme of lecanemab includes one Open-label Extension of the Phase 2 study (Study 201 OLE) and one Open-label Extension of the Phase 3 study (Study 301 OLE).

Study 201 OLE

Any subject who completed Visit 42 (Week 79) of the Core Study 201 had the option to participate in the OLE Phase. Subjects who previously completed the Core Study (through the Follow-Up Visit, Visit 43 [Week 90]) and/or fulfilled the OLE Phase inclusion and exclusion criteria were eligible to participate. Subjects who discontinued the Core Study were eligible to participate in the OLE Phase, provided they met the inclusion and exclusion criteria for the OLE Phase.

The OLE was initiated after analysis of the Core Study was complete and CSR finalised, resulting in an average 24-month Gap Period off study drug between the final visit in the Core Study (Visit 42 [Week 79]) and OLE Baseline Visit.

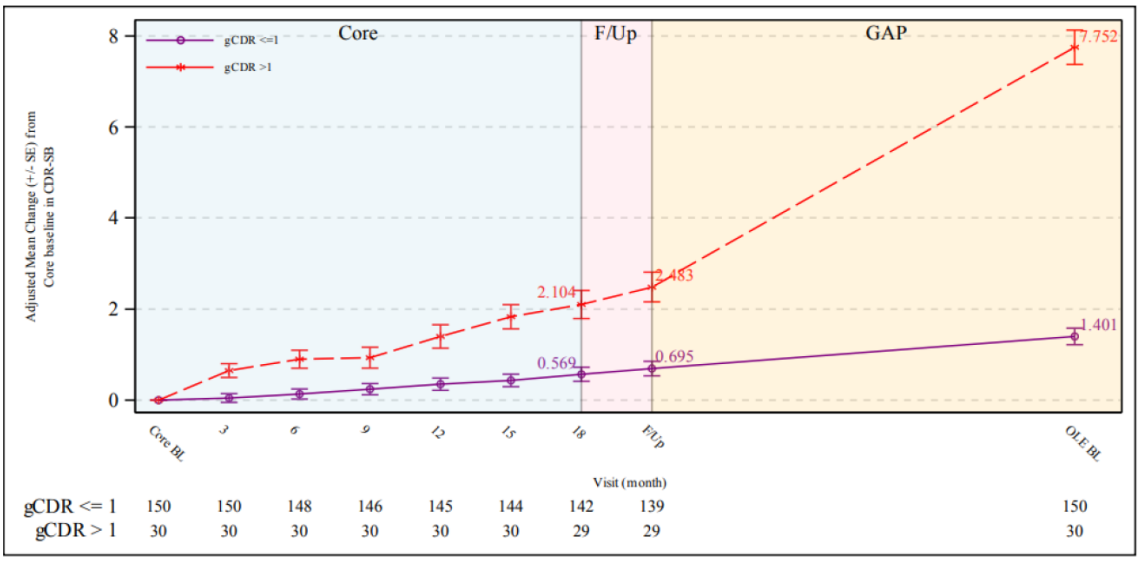


Figure 21 shows the adjusted mean change from Core Baseline (by visit and global CDR group) for the Core Study and Gap Period for ADCOMS, CDR-SB.

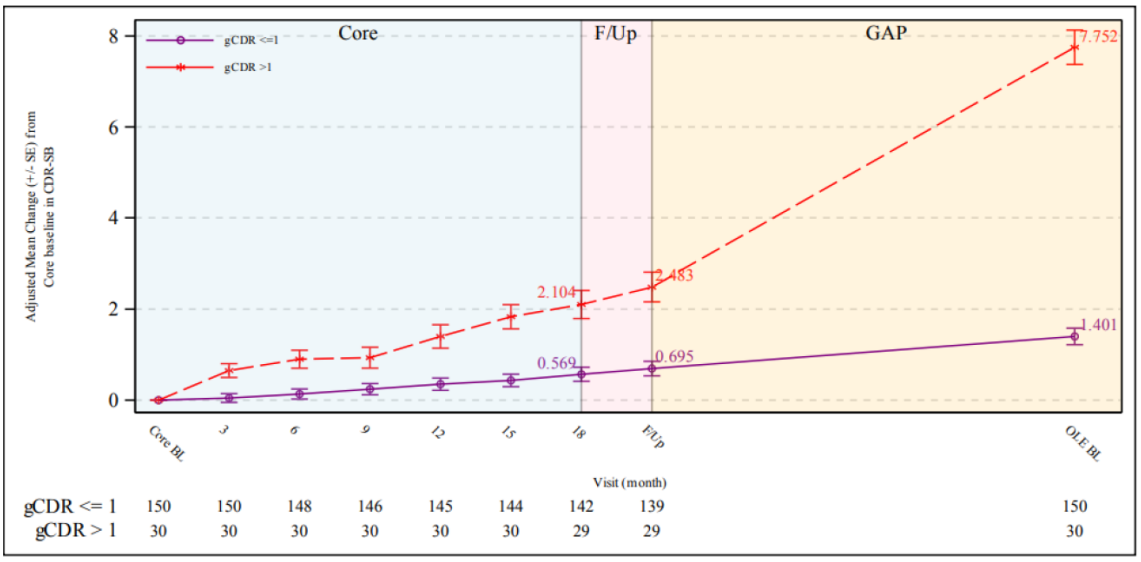


Figure 21. Line plot of adjusted mean change (± SE) from core baseline in CDR-SB by visit and global CDR group – MMRM – core study and gap period (OLE enrolled set)

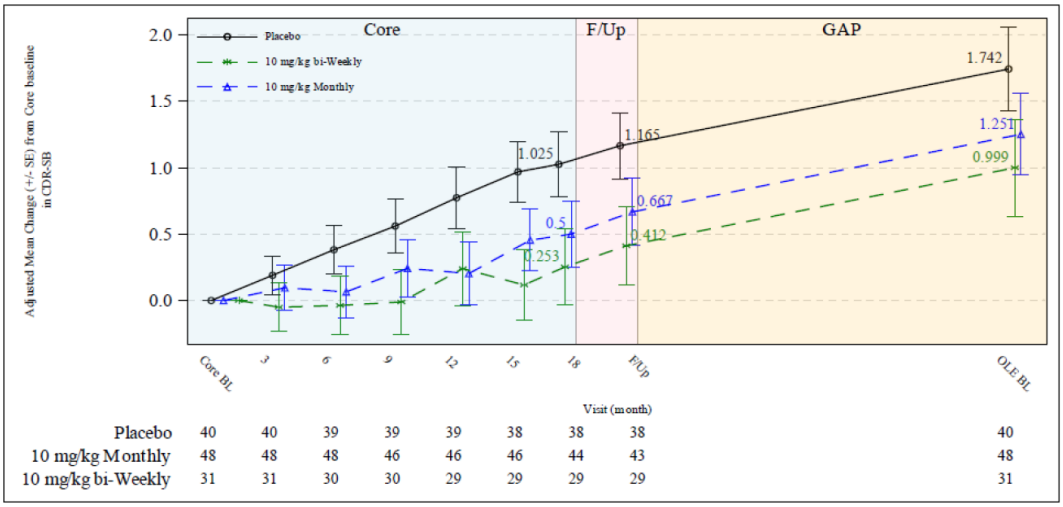


Figure 22 shows the adjusted mean change from Core Baseline (by visit) for the Core Study and Gap Period for CDR-SB, for the OLE Enrolled Set excluding those who progressed beyond EAD (global CDR score >1 at OLE Baseline).

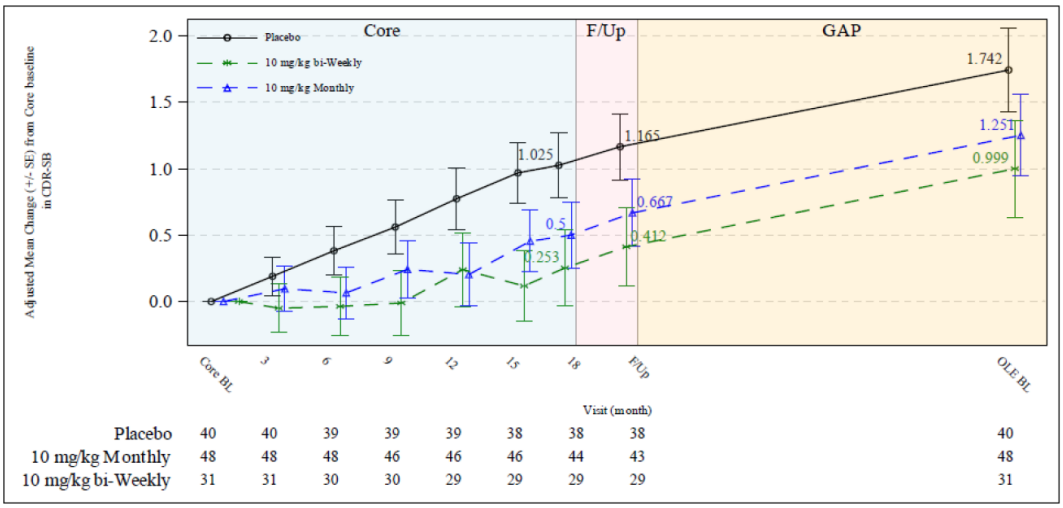


Figure 22. Line plot of adjusted mean change (± SE) from core baseline in CDR-SB by visit – MMRM – core study and gap period (OLE enrolled set excluding those who progressed beyond EAD)

Study 301 OLE

No efficacy data are reported in the provided interim CSR. With the latest responses during the assessment procedure, the applicant has updated the efficacy data from the Study 301, with a comparison between early- and late-starters. Only graphic representation has been provided without any tabulated data.

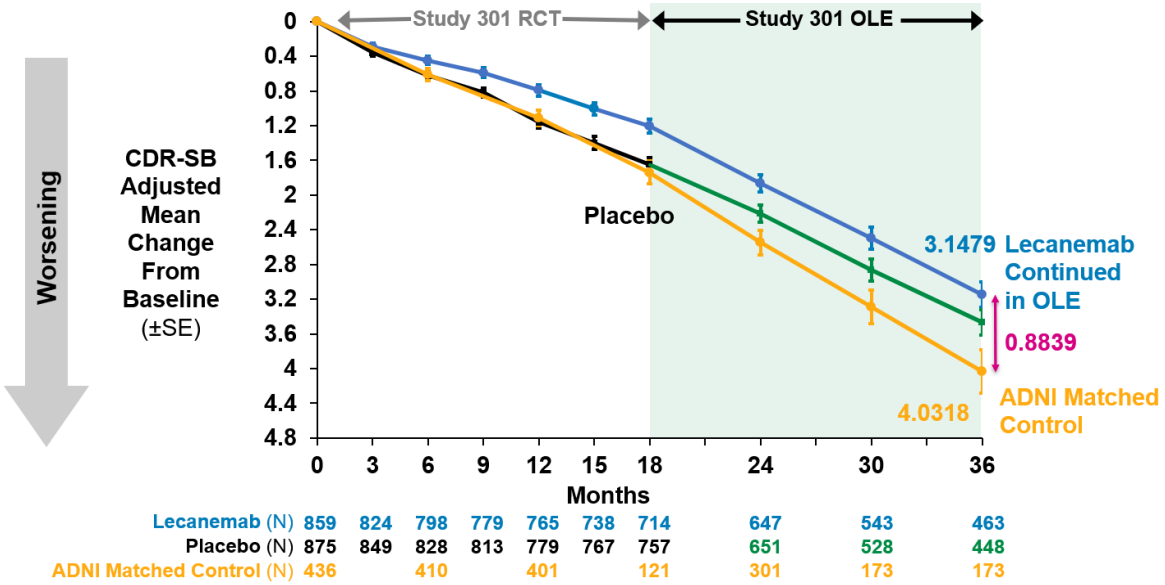


Figure 23. Adjusted mean change (±SE) from baseline in CDR-SB in context of observational cohort through 36 months – study 301 core and OLE phase (ITT FAS+)

ADNI = Alzheimer's Disease Neuroimaging Initiative, CDR-SB = Clinical Dementia Rating –Sum of Boxes, FAS+ = full analysis set+, OLE = open-label extension, SE = standard error.

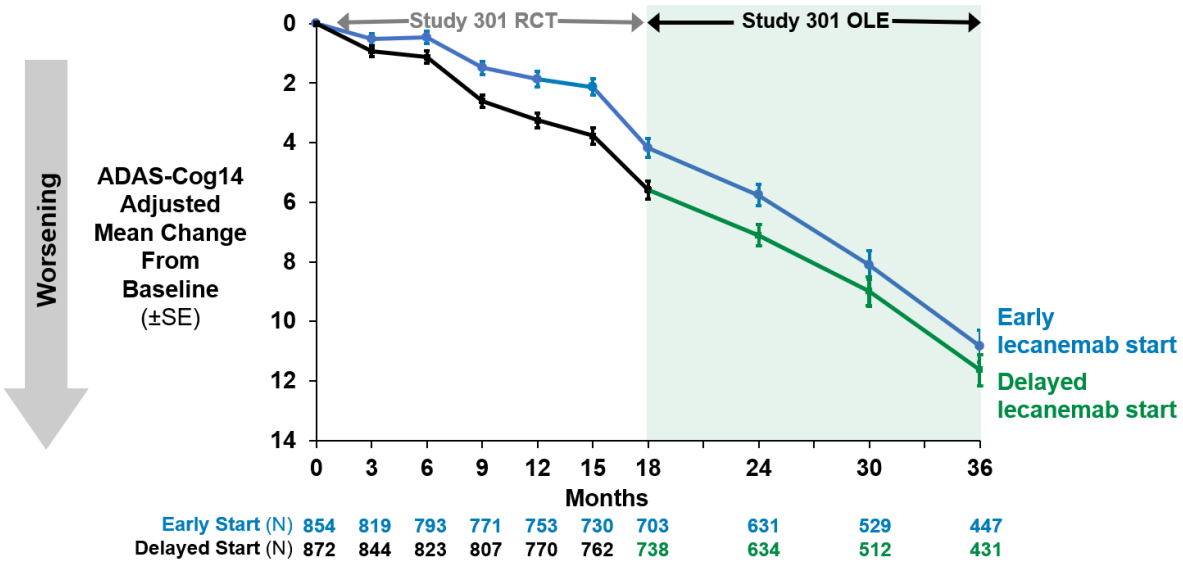


Figure 24. Adjusted mean change (±SE) from baseline in ADAS-Cog14 – study 301 core and OLE phase, intent to treat (full analysis set+)

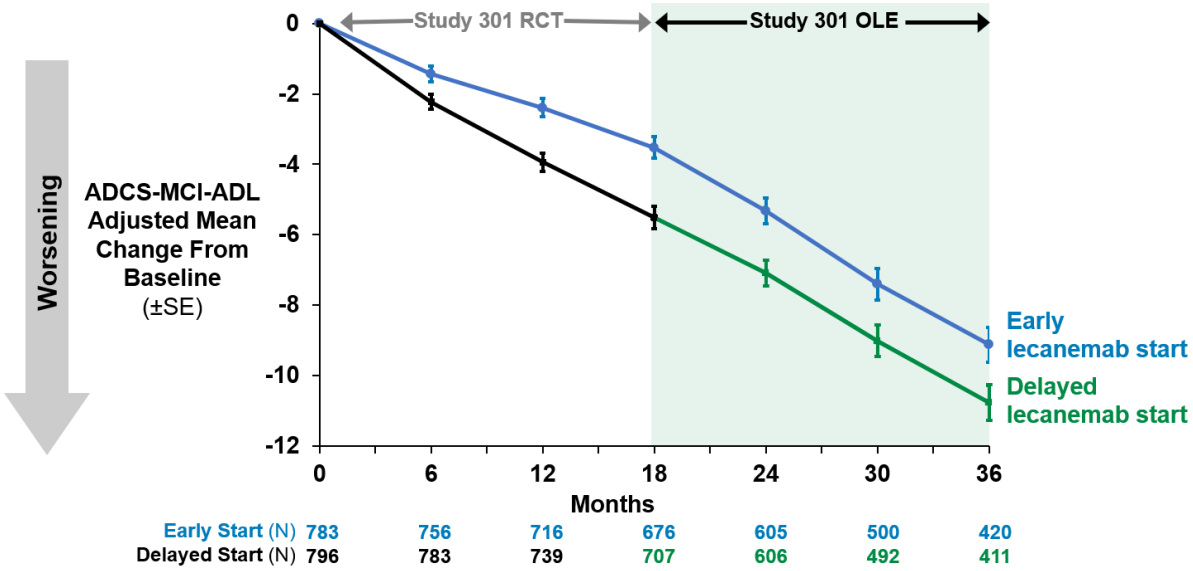


Figure 25. Adjusted mean change (±SE) from baseline in ADCS-MCI-ADL – study 301 core and OLE phase, intent to treat (full analysis set+)

2.6.6. Discussion on clinical efficacy

The evidence of efficacy of lecanemab in the intended indication is based on data from 18-months double-blind and placebo-controlled phase of a single pivotal, phase III trial which investigated 10 mg/kg biweekly lecanemab infusions versus matched placebo (Study 301 Core).

The maintenance of the effect (beyond 18 months) is be based on the ongoing open label phase of the Study 301 (Study 301 OLE) with an intended duration up to 4 years. However, limited efficacy data is available from the extension phase of the study.

Study 201 (Core + OLE phases) is considered as a small size dose finding study with supportive open-label data on retreatment and maintenance of efficacy in the absence of efficacy data from OLE phase of Study 301. For reasons discussed below, it is not considered confirmatory.

In the clinical development programme, it has not been taken into consideration that two confirmatory trials are recommended for treatment areas such as AD. With reference to the Points to consider on applications with […] one pivotal study, the need for replication is particularly relevant – among others – in therapeutic areas with a history of failed studies or failures to confirm seemingly convincing results (such as Alzheimer's Disease).

The recommended dose of lecanemab is 10 mg/kg administered as an intravenous (IV) infusion over approximately one hour, once every 2 weeks. Continuous treatment is recommended until progression into moderate AD stage. No data (e.g. randomised withdrawal) has been provided to justify criteria to stop treatment.

Design and conduct of clinical studies

BAN2401-G000-201 (dose-finding)

The trial was conducted in subjects with Mild Cognitive Impairment due to AD and in subjects with mild AD and having a positive biomarker for brain amyloid pathology. Overall, selection criteria are acceptable, including diagnosis based on NIA-AA core clinical criteria and enrolling both ApoE4 carriers and non-carriers.

5 doses/regimens were investigated: 2.5, 5, or 10 mg/kg given biweekly (i.e. every two weeks), or 5 or 10 mg/kg given monthly.

Overall, the primary endpoint (i.e. change in ADCOMS at Month 12), and the key clinical secondary endpoints (i.e. change in ADCOMS, CDR-SB, and ADAS–Cog14 at Month 18) and key PD secondary endpoints (i.e. change in amyloid PET, CSF Aβ[1-42], CSF t-tau, and CSF p-tau, and in total hippocampal volume using vMRI at Month 18) are acceptable for the dose-finding purpose of this Phase 2 study. However, it is important to note that co-primary objective of the double-blind period of the dose finding study is based on a different clinical efficacy endpoint evaluated at a different time point than the primary analysis of the single pivotal trial. Moreover, as highlighted for the Phase 3 study, this primary endpoint (i.e. ADCOMS) is not validated.

Importantly, methodological issues make the results exploratory only, in particular: the lack of control of the alpha risk (including that analyses have not been adjusted for multiple comparisons), the use of a Bayesian response adaptive randomisation, and the change in randomisation strategy to exclude ApoE4 carriers from the highest dose of 10 mg/kg biweekly. Indeed, randomisation strategy was changed while the study was ongoing to exclude ApoE4 carriers from the highest dose of 10 mg/kg biweekly, because a higher risk of developing symptomatic amyloid–related imaging abnormalities with cerebral oedema (ARIA–E).

BAN2401-G000-301 (pivotal)

The overall design of the randomised, double-blind, placebo-controlled Phase 3 study was overall acceptable.

The study population was subjects presenting MCI due to AD, with a CDR score of 0.5, or subjects presenting mild AD, with a CDR score of 0.5 to 1.0, and having a positive biomarker for brain amyloid pathology. Diagnosis was based on NIA-AA core clinical criteria. Male and female aged ≥50 and ≤90 years could be enrolled, and selection criteria required a MMSE score ≥22 and ≤30. Finally, ApoE4 non-carriers and ApoE4 carriers were allowed to enter in the study, ApoE4 being the major genetic determinant of Alzheimer's disease. Overall, the selection criteria are acceptable. However, the amyloid pathology inclusion criterion raise concern. As mentioned in the EMA guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease (CPMP/EWP/553/95 Rev.2), CSF and PET amyloid biomarkers are strongly correlated, however it is not clear how much this depends on the type of assay and the cut-off. Thus, the absence of specified cut-offs defining brain amyloid pathology measured by amyloid PET or t-tau/Aβ in CSF raises concern on the homogeneity of the population selected. Indeed, the inclusion criterion requires only to present a "positive biomarker", which remains vague. In the answer to a question, the applicant indicated that cut-off values were pre-specified for entry criteria, originally at >0.37 and later changed to >0.54. In answer to further questions, the applicant explained that this change was due to re-standardisation of the Ab 1-42 assay. Subsequently, the applicant provided further explanation on the validation of the CSF cut-off. The pre-specified value was established based on 3 cohorts (i.e. 2 from Eisai studies [Study 201 from the lecanemab clinical programme, and Study E2609-G000-301/302 from the Elenbecestat clinical programme], and on from the Washington University Knight Alzheimer Disease Research Center), and validated with a fourth cohort (i.e. Study E2609-G000-301/302 from the Elenbecestat clinical programme). Additionally, although NIA-AA criteria are mentioned in description of the population studied in the SmPC, the biomarker support is not a requirement for clinical diagnosis according to these criteria and should be reflected as a requirement used for inclusion into the pivotal study in the SmPC.

Additionally, patients included in the lecanemab trials were in the early symptomatic stages of late age-of-onset AD, due to the age limits mainly, despite the fact that genetic forms of the disease were not listed in the exclusion criteria. Patients with autosomal dominant AD or with Down syndrome frequently present as early age-of-onset AD and are known to be associated with a higher rate of cerebral amyloid angiopathy and possible ARIA events. The safety and efficacy of lecanemab in early age-of-onset AD population is unknown, however, its use is not limited by clinical or imaging criteria in the proposed SmPC. The Applicant informed that patients with genetic forms of AD were not treated with lecanemab in the pivotal studies and the ongoing studies (Study 303 and DIAN-TU) are intended to assess the efficacy of lecanemab in the preclinical AD and DIAD populations. Lecanemab is not being studied in patients with Down syndrome. The Applicant agreed to include proper warnings in section 4.4 of the proposed SmPC as requested.

Similarly, patients included in the lecanemab trials had relatively typical forms of memory-predominant AD. Patients with atypical AD syndromes including logopenic variant primary progressive aphasia, posterior cortical atrophy, or behavioural or dysexecutive AD were not specifically excluded from the lecanemab trials, however, the safety and efficacy of treatment in patients without memory-predominant AD are not equally characterised.

The dose used in the active arm was 10 mg/kg biweekly (i.e. every two weeks). As discussed below, this dose presents unacceptable risks particularly for APOE4 homozygous carriers (about 15% of AD population). No other dose for this sub-population could be justified. Consequences of this relate more closely to safety and benefit/risk aspects and are discussed in the respective sections. The comparator

used in the control arm was a placebo which is acceptable in absence approved treatment in the claimed disease modifying indication for AD.

The primary endpoint was the change from baseline in the CDR-SB (clinical dementia rating sum of boxes) at 18 months, in a superiority setting compared to placebo. The endpoint is agreed, as well as the timepoint which appears sufficiently late as per as the EMA guideline (CPMP/EWP/553/95 Rev.2).

The first key secondary endpoint was the change from baseline in amyloid PET using centiloids at 18 months. It is agreed that assessment of the brain amyloid level is of importance with respect to the mechanism of action, and the need to characterise the relationship between changes in amyloid and clinical outcomes, which has not been yet established. The key clinical secondary endpoints were ADAS-Cog14, ADCOMS, and ADCS MCI-ADL, also assessed at Month 18. Overall, the selected outcomes and the testing hierarchy are acceptable and in line with SAWP's position (EMA/SA/0000088736). However, as emphasised in a previous Qualification Advice (EMA/CHMP/SAWP/773528/2014), and confirmed by the applicant in the answer to the questions, ADCOMS is not a validated endpoint.

An important point is that the main efficacy evidence comes from a single confirmatory trial. As mentioned above, a therapeutic area with a history of failed studies or failures to confirm seemingly convincing results is not suitable for such an approach. Moreover, study results are expected to be particularly compelling with respect to clinical relevance, statistical significance, generalisability and internal consistency.

The anticipated treatment difference (for sample size determination) between lecanemab and placebo for the change from baseline in CRD-SB was 0.373. However, the CHMP previously noted (EMA/SA/0000077368), that an effect size < 0.5 points "would raise a discussion with respect to the clinical relevance of the effect if this is not further supported by the other secondary clinical outcomes".

The Applicant described that "randomisation was managed" so that no less than 70% of the total number of subjects would be APOE4 carriers, and no less than 50% in the MCI due to AD clinical subgroup. The Applicant confirmed that no operational intervention or capping was in the end implemented for clinical subgroups (proportions were nevertheless in line with the protocol). It was also clarified that the APOE4 carrier status restriction was implemented during the last 3 months of screening only. The proposed stratification factors (i.e. the use of AD symptomatic medication at baseline, the APOE4 carrier status and the geographical region) are supported. No relevant justification has been provided for the absence of gender in the stratification procedure, but the applicant performed additional analyses adjusting for sex which showed consistent results.

Blinded medical monitoring team reviewed amyloid-related imaging abnormalities (ARIA), infusion-related reactions and hypersensitivity reactions. In the event that emergency conditions required knowledge of the study drug given, the blind could be broken. While the limited number of subjects (6) is unlikely to affect study conclusions, this highlights the need for more conservative handling of missing data, particularly in case of adverse events.

The primary population is ITT FAS+ for EMA and PMDA, whereas a different dataset was used for other regions. This is related to the handling of the approximately 200 subjects who were randomised to compensate the lack of power induced by 200 subjects having missed 3 or more consecutive doses due to the COVID-19 pandemic. In a previous request for scientific advice, the applicant suggested to exclude the 200 subjects with 3+ missed consecutive doses from efficacy analyses and to replace them with the 200 newly enrolled subjects (which corresponds to the definition of the dataset for other regions). This proposal was not supported by the CHMP, because their replacement would have relied "on the strong and untestable assumption that missed consecutive doses can be solely attributed to closure of the study sites independent of any other patient factor". Instead, the inclusion of the

additional 200 subjects in the primary analysis (i.e. without excluding other subjects) was acceptable to the CHMP, which explains the separate definition of ITT FAS+ for EMA.

The definition of the ITT FAS+ excludes patients who did not receive at least 1 dose of study drug, or who did not have both a baseline and at least one post-baseline primary efficacy measurement. While this does not follow the intent-to-treat principle, it is noted that an additional analysis of the primary endpoint has been performed based on all randomised subjects.

The hierarchical testing procedure that was implemented across primary and secondary endpoints ensures in principle the overall control of the study type I error.

There is no detailed description provided of estimand attributes nor of the strategy for handling intercurrent events. It is understood that three intercurrent events (ICE) were identified (initiation of new AD concomitant treatment or change of AD concomitant treatment or treatment discontinuation) and that all observed data were included regardless of these events, as a proposed estimator for a treatment policy strategy. This is acceptable.

Supplementary analyses were performed by the applicant where data were excluded (and treated as if missing at random through the MMRM analysis) after initiation/dose adjustment of symptomatic AD drug or treatment discontinuation. Similar analyses were also provided with the exclusion of data after the occurrence of ARIA events.

In relation to presence of ARIA, the applicant argued that steps have been taken to avoid functional unblinding. In order to assess the potential bias associated with potential unblinding due to ARIA, the applicant was asked to perform sensitivity analyses using a more conservative assumption for missing measurements following ARIA events.

The Applicant clarified that only 48% and 31% of patients who discontinued treatment in the lecanemab and placebo groups respectively provided post-discontinuation data for the primary analysis model. The rest of the data were handled as missing observations in the MMRM which did not include an on/off treatment indicator. The handling of missing data raises concerns. Indeed, missing data are not imputed in the primary and key secondary analyses. They are therefore handled through the use of the MMRM which assumes missing at random (MAR) data. However, this is a questionable assumption as some data are very likely to be missing not at random (MNAR). The sensitivity analysis using rank ANCOVA after MI also assumes MAR and therefore does not address this specific issue. The tipping point analysis is helpful in determining the level of the shift parameter (used for missing data imputation) that would be required to lead to a non-significant statistical result. If measurements after discontinued study medication are missing, it is reasonable to assume that patient in the active arm do not continue to benefit from the study medication after discontinuation. Moreover, missing outcomes on the cognitive endpoints for patients who discontinued the study due to ARIA-E and ARIA-H can be expected to be worse than for patients in the reference arm.

The applicant was requested to repeat the primary and key secondary analyses (the same MMRM analyses for changes from baseline) using a more conservative imputation of missing data. For patients who discontinued the study due to ARIA-E and ARIA-H, missing measurements were imputed with a worst-case scenario (i.e. worst change from baseline across treatment arms at the corresponding time point). For all other missing values, reference-based multiple imputation should be used. It was concluded from the applicant's response that, although a potential impact of ARIA events on cognitive worsening cannot be excluded, it appears to be limited, although this is only within the observed 18-month study period, and significant uncertainties persist on the longer-term consequences. The additional sensitivity analyses, together with the description of efficacy post-ARIA occurrence, provided reassurance on the statistical robustness of efficacy results. It is accepted that

the sensitivity analyses that were provided using control-based MI for all missing measurements appear to be sufficiently conservative.

Sensitivity analyses based on log-transformed values or based on the ranks were also planned to assess the robustness of the primary approach (based on the natural scale) in case of deviation from the normality assumption.

It is noted that modifications were made to the planned analyses on several occasions, either as part of protocol amendments or SAP revisions. More specifically, the key secondary and secondary endpoints were changed while the study was ongoing, with protocol amendment 8 and 9. Another consequence was the modification of the statistical testing strategy. The changes were discussed in a previous scientific procedure (EMA/SA/0000077368) and follow up request for clarification (EMA/SA/0000088736). Although CHMP highlighted that any late changes to the testing strategy were generally discouraged (and although a different ordering would have been preferred), the updated set of key secondary endpoints was thought to be acceptable. Considering previous CHMP feedback on study endpoints, and given the double-blind status of the trial, these modifications are not thought to have had a significant impact on the reliability of the study results.

Efficacy data and additional analyses

BAN2401-G000-201 (dose-finding)

In total, 856 subjects were randomised: 247 in the placebo group, 52 in the group 2.5 mg/kg biweekly arm, 51 in the in the 5 mg/kg monthly group, 92 in the 5 mg/kg biweekly group, 253 in the 10 mg/kg monthly group and 161 in the 10 mg/kg biweekly group.

Regarding the baseline and demographic characteristics, no critical difference was observed for the majority of the parameters. However, because of the change of the randomisation strategy, there was an important imbalance in ApoE4 status, with a lower proportion of ApoE4 carriers in the 10 mg/kg biweekly arm (i.e. 30.3% versus from 71.0% to 91.0% in the other arms). This makes difficult the interpretation of the results in the full population. Additionally, it can be noted that there is a higher proportion of Mild AD in the 5 mg/kg biweekly and 10 mg/kg biweekly arms (respectively 41.6% and 40.8%) compared to the placebo, 2.5 mg/kg biweekly, 5 mg/kg monthly and 10 mg/kg monthly arms (35.3%, 34.6%, 31.3% and 32.5%).

The primary endpoint was not met: the final posterior probability to show a 25% reduction in ADCOM at Month 12 for 10 mg/kg biweekly in comparison with placebo was 58.5%, below the 80% threshold. The highest point estimate was though seen in the highest dose (10 mg/kg biweekly).

Regarding subgroup analysis by clinical status, as expected, the size of the effect is larger in subjects with Mild AD than with MCI due to AD, given that a higher rate of worsening is anticipated for Mild AD. Regardless the subset, the larger size effect in change from baseline in ADCOMS at Month 12 remains for the 10 mg/kg biweekly arm.

Regarding subgroup analysis by ApoE4 status, the results remain also in favour the 10 mg/kg biweekly dose. Additionally, it is observed a larger size effect in ApoE4 carriers than in ApoE4 non-carriers for the 10 mg mg/kg biweekly dose in change from baseline in ADCOMS at Month 12: the LS mean difference (95%CI) versus placebo is respectively -0.091 (-0.161, -0.022) and -0.014 (-0.061, 0.034). The answer in ApoE4 non-carriers is besides worse than placebo for all the 4 lower doses.

The results for the key clinical secondary analysis, all assessed at Month 18, were overall in favour of a larger efficacy for the 10 mg/kg biweekly dose. However, unexpected results for the lowest 2.5 mg/kg biweekly dose compared to the higher dose, in particular in subgroup analysis by ApoE4 status, raises

question on the dose-response effect. Looking at within ApoE4 carriers, the curve of 10 mg/kg biweekly dose seems separate from the other doses from Week 27 for the heterozygotes. However, for homozygotes, no trend emerges. Additionally, the response in ApoE4 non-carriers appears quite limited, or even worse than placebo as in change from baseline in CDR-SB at Month 18.

Regarding the biomarkers, the highest reduction in mean change from baseline in brain amyloid levels measure by amyloid PET is observed for the 10 mg/kg biweekly, although mitigate by the non-demonstrated PD/clinical effect relationship.

In conclusion, the failed primary endpoint together with the several important methodological issues make the results of this dose-finding Phase 2 study purely exploratory only. Moreover, the important imbalance proportion of ApoE4 carriers makes difficult to interpret the primary and the key clinical secondary analysis for the 10 mg/kg biweekly dose in the overall population. However, the subgroup analyses by ApoE4 status suggest a larger efficacy for the highest dose (10 mg/kg biweekly). Additionally, the greatest reduction in brain amyloid levels has been observed for the highest dose, although mitigate by the non-demonstrated PD/clinical effect relationship. However, the answer in ApoE4 non-carriers appears quite limited, or even worse than placebo as in change from baseline in CDR-SB at Month 18. Moreover, several results for 2.5 mg/kg biweekly dose raise concerns on the dose-response effect, this is specially the case for ApoE4 homozygotes.

BAN2401-G000-301 (pivotal)

5967 subjects were screened for enrolment leading to 1795 randomised subjects and 4172 screen failures (70.0%). The main reason for failure was to not meet selection criteria (59.6%). This appears unexpectedly high. In the answer to CHMP questions, the applicant indicated that similar screen failures have been reported for other recently completed AD studies. The highest reason for screen fail (51%) was not meeting the cognition criteria (i.e. patients screened resulted unimpaired or having moderate-to-severe AD). The second reason was the lack of amyloid on PET (17%). Among the 1795 enrolled subjects: 897 were randomised in the placebo group, and 898 were randomised in the lecanemab group. It is to note that the experts of the SAG were concerned about the generalizability of the observed results as they noted that a relatively low percentage of the population (10-15%) could be eligible for the medicinal product.

In general, the conduct of the study does not raise important issues. However, ADCS-MCI-ADL was upgraded from an exploratory to a key secondary endpoint late in the study (i.e. in Feb 2022 while the study ended in Aug 2022). In contrary, ADCOMS was downgraded from a key secondary to other secondary endpoint (at the time), and then, ultimately re-upgraded as the 3rd key secondary endpoint. Although no chronology was provided, the applicant justified the change in key secondary objectives by interactions with Health Authorities.

Overall, the demography and baseline characteristics were well balanced across the two arms, including for ApoE4 carriers (68.1% in the lecanemab arm versus 69% in the placebo arm), the clinical subgroups (61.9% of MCI in the lecanemab arm versus 61.5% in the placebo arm), gender (53.1% of women in the lecanemab arm versus 51.4% in the placebo arm), and AD symptomatic medication (53.2% in the lecanemab arm versus 51.9% in the placebo arm). There is no concern for either main clinical outcomes or biomarkers.

Regarding concomitant symptomatic AD medication during the study, the use is overall similar across the two arms and might unlikely have impacted the efficacy results.

The primary analysis, conducted in a superiority setting in the ITT population, showed a statistically significant difference of -0.451 (95%CI: -0.669, -0.233; p=0.00005) between lecanemab and placebo in change from baseline in CDR-SB at 18 months. The mean (SD) change at Week 79 from baseline was +1.21 (0.08) (with a mean [SD] baseline value of 3.18 [1.34]) for the lecanemab group, and

+1.66 (0.08) (with a mean [SD] baseline value of 3.22 [1.34]) for the placebo group. As a reminder, CDR-SB grades from 0 to 18 (sum of the score in 6 items grading from 0 to 3); a difference -0.451 can be viewed as a limited benefit. Moreover, conservative estimation makes the benefit even more uncertain; updated analyses show that the effect size ranges between 0.23 and 0.47 for the sensitivity analyses with the worst- and best-case scenarios of missing data for the primary analysis of CDR-SB changes over 18 months. As mentioned above in the context of the sample size calculation, the CHMP previously noted (EMA/SA/0000077368), that an effect size < 0.5 points "would raise a discussion with respect to the clinical relevance of the effect if this is not further supported by the other secondary clinical outcomes". On the same note, in the context of a Advice on the development of ADCOMS, in 2014, the CHMP expressed the view that a 25% reduction in deterioration – then assumed equivalent to 1.1 point reduction in ADAS-Cog for Prodromal AD subjects at 24 months and 2.5 point reduction in ADAS-Cog at 24 months for mild AD dementia subjects – would be barely meaningful and only acceptable if supported by other clinical endpoints. It is also important to note that – while the effect at 18 months is expressed in terms of absolute difference or in % of decline prevented, the hypothesis that the latter is constant over time (hence leading to an increase in absolute difference) is not corroborated by the available data (see for example 301 OLE preliminary results above).

Overall, it is agreed that the primary analysis is statistically significant, but this is not sufficient. It is important that the effect size is of a certain magnitude. All the more in the context of a single pivotal study where particularly compelling clinical results are awaited. However, a benefit deriving from a difference in CDR-SB < 0.5 points is small and not considered sufficient. It is also reminded that the study has been powered to show a small effect size (i.e. a difference of 0.337 in CDR-SB); this further suggests not to over-interpret the statistical significance. Moreover, the SAG-N experts considered by consensus that the above-mentioned observed differences in favour of Leqembi are n*ot clinically relevant and meaningful for the patients*. The SAG-N experts noted that the minimally clinically important differences (MCID) for CDR-SB are 1 point and between 1 and 1-2 points for mild cognitive impairment (MCI) due to Alzheimer Disease (AD) and mild AD, respectively. Additionally, the patient representatives who participated to the SAG agreed with the above views. In the view of these patient representatives, the magnitude of the above-mentioned effect is not expected to significantly impact the life of patients.

Furthermore, the SAG underlined that the potential of functional unblinding due to the relatively large proportion of infusion-related AEs was highlighted, which is particularly relevant in the case of a caregiver-informed primary outcome. This could have contributed to the observed difference between those in the Leqembi arm compared to the control group.

Looking at the results by domain, difference in CDR-SB seem not driven by one or several domains. Difference in mean change from baseline at Month 18 is slightly less or less than - 0.1; for instance, the difference in memory at Month 18 is -0.077 (IC95%: -0.123, -0.031). This is considered as a small effect.

The applicant has presented several progressor analyses (RR at 18 months) that evaluate different worsening cut-offs of the endpoints (CDR-SB and others). The absolute difference to placebo appears to be modest at all thresholds of CRD-SB score. These data are not type I error controlled and they in any case do not refute the conclusion that absolute differences to placebo are of small magnitude.

Additionally, the results of the key clinical secondary endpoint provide a limited support to the limited primary results demonstrating the efficacy of lecanemab.

The second key secondary analysis shown a statistically significant difference of -1.442 (95%CI: -2.270, -0.613; p=0.00065) between lecanemab and placebo in change from baseline in ADAS-Cog14 at 18 months. To put this difference in context, a 4-points difference at 6 months has been found – based on symptomatic treatments – to be clinically meaningful. (Rockwood 2010, DOI:

10.1002/gps.2319). Even if the early AD population is taken into consideration, 1.4 points difference is considered very limited to reach clinical relevance. An MCID of 3 points on ADAS-Cog13/14 is recommended for mild AD (Schrag 2012, DOI: 10.1136/jnnp-2011-300881) and 2 points for MCI due to AD (Lansdall 2022, DOI: https://doi.org/10.14283/jpad.2022.102). In previous trials with anti-amyloid therapies, in the placebo group, LS mean change score (SD) of ADAS-Cog14 over 80 weeks was observed as 4.1 points (9.5) in patients with CDR=0.5 at baseline, and 5.2 points (9.6) in patients with mild AD (Wessels 2015, doi: 10.14283/jpad.2015.82).

The third key secondary analysis shown a statistically significant difference of -0.050 (95%CI: -0.074, -0.027; p=0.00002) between lecanemab and placebo in change from baseline in ADACOMS at 18 months. In a Qualification Advice (EMA/CHMP/SAWP/773528/2014) mentioned above, the CHMP emphasised that a 0.06 reduction on ADCOMS (i.e. targeted size effect in MCI due to AD during the development) is equivalent to a 1.2-point reduction in ADAS-Cog, which is considered as an effect of small magnitude. Thus, the clinical relevance of the result is questionable. Moreover, given that the endpoint is not validated, the result is exploratory.

Finally, the last key secondary analysis shown a statistically significant difference of 0.797 (95%CI: 0.274, 1.321; p=0.00284) between lecanemab and placebo in change from baseline in ADCS MCI-ADL at 18 months. However, it is unclear how relevant is the effect size. The arguments provided in the answers to questions did not allow to further justify the clinical relevance.

The SAG also noted that the small difference in CDR-SB is in line with the small difference on key secondary outcomes, including ADAS-Cog, for which the MCID is around 3-4 points (Molnar FJ, JAGS 2009), whereas the difference between the Leqembi group and the placebo group was 1.44 points.

Another question is the relationship between pharmacodynamics outcomes and clinical outcomes. Indeed, to date it is unclear whether a reduction in brain amyloid level corresponds to sufficient clinical improvement.

It is acknowledged that results suggest a clear reduction in PET Amyloid following treatment in the lecanemab group at Month 18, while the level in the placebo group remained stable. Additionally, beyond Week 53, the brain amyloid level passed below the positivity threshold, which is defined as 30 centiloids according to the applicant. However, the correlations results between change from baseline in amyloid PET using centiloids at week 79 and change from baseline in main clinical endpoints at week 79 do not suggest a relevant relationship between this biomarker and CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL. As a matter of fact, the correlation between change from baseline in amyloid PET using centiloids at week 79 and change from baseline in CDR-SB at week 79 is, respectively with Pearson method and Spearman method: -0.165 and -0.277 for the lecanemab arm, and -0.053 and 0.005 for the placebo arm. While larger than for placebo, the strength of the relationship for lecanemab remains limited. Moreover, while the graphic curve suggests a slow in brain amyloid level decrease after 1 year, the CDR-SB curve of patients treated with lecanemab seems have a quite linear rate of worsening beyond Week 39. Moreover, the trajectory of the CDR-SB curve suggests thus that patients are still worsening, with a maintained rate, while the negativity in brain amyloid level has been reached. Although a reduction in brain amyloid was observed, the poor correlation between brain amyloid load and clinical endpoints does not allow to establish that the amyloid reduction can support clinical benefit. Moreover, the experts of the SAG noted also the lack of association between the changes on pathology (B-amyloid load) and the changes in the cognitive function at the individual level.

The Applicant provided further scatter plots, correlation analyses and analyses using Prentice criteria. It was determined that the applicant's approach to patient-level "model-based" correlation (based on predicted values) was not interpretable. The patient-level correlation analyses provided in the initial dossier are considered reliable, and showed poor levels of correlation, across and within treatment

arms, at all investigated time points. The Applicant's approach to population-level correlation analysis is not objected to in principle. However, the resulting population-level correlations are based on only 6 data points from the same two studies (i.e. 4 from study 201 and 2 from study 301). The mediation analyses have also been described. It is acknowledged that the proportion of treatment effect on clinical endpoint that is explained by the biomarker change in the statistical model used by the applicant is 80%. However, it is difficult to interpret this result in the context of the poor patient-level correlation that has been observed in the same study. In this context, the population-level correlations and the results from the mediation analyses are hypothesis-generating at best, and the potential surrogacy of amyloid PET cannot be considered demonstrated. An important point is also to which extent lecanemab is efficacious in ApoE4 carriers. Indeed, on one hand, ApoE4 is an important risk factor for AD; on another hand, the hypothesis of the applicant (as stated in a previous scientific advice (EMA/SA/0000077368)) was that the effect of lecanemab might be larger in this subset, as ApoE4 carriers have more soluble Aβ aggregate species which are toxic to synapses as compared to ApoE4 non-carriers, thus favouring more cell degeneration and death. The Applicant argued this mechanism of action would be more suited to ApoE4 carriers as compared to the overall AD population. However, while a larger effect was seen in ApoE4 in Phase 2 dose-finding study, the Phase 3 study results suggest surprisingly a reduced difference in this population. Indeed, the mean difference versus placebo in change in CDR-SB from baseline at Month 18 was smaller in ApoE4 carriers (-0.33) than in ApoE4 non-carrier (-0.75). Moreover, looking at the sub-strata, a mean difference versus placebo of -0.50 is seen in ApoE4 heterozygous, while mean difference versus placebo of +0.28 is seen in the ApoE4 homozygous, meaning a worse answer than placebo for homozygous. Additionally, similar subgroup's observation are made for other clinical endpoints (i.e. ADAS-Cog14, ADCOMS and ADCS MCI-ADL). Overall, this raises strong concerns on the benefit in ApoE4 carriers, especially homozygotes, while this population is particularly at risk and this is contradictory with the applicant's PD hypothesis. Indeed, in the previous Scientific Advice, the applicant argued that the effect of lecanemab might be larger as ApoE4 carriers have more soluble Aβ aggregate species which are toxic to synapses as compared to ApoE4 non-carriers thus favouring more cell degeneration and death, and this granulate difference in mechanism of action is more suited to ApoE4 carriers as compared to the overall AD population. Applicant has been asked about potential explanations for this unanticipated result, including the possibility that this be mediated by dose interruptions due to ARIA (see below). The Applicants responded that the homozygous constituted a small subgroup (i.e. 132 and 136 subjects in the placebo and lecanemab groups respectively) and that "placebo homozygous APOE4 carriers in CDR-SB was unexpectedly slower than in heterozygous and non-carriers". While it is acknowledged that a slower deterioration gives less room to show an efficacy, this explanation appears insufficient. First, there is no evidence that the natural course of the disease in homozygous differ between the placebo and the lecanemab group. Additionally, it should be emphasized that the change in amyloid PET at Month 18 seems higher in APOE4 carriers, both heterozygous and homozygous, than non-carriers. This raises further uncertainties on the correlation between amyloid reduction and clinical outcomes.

Additionally, uncertainties of the results observed in patients below the age of 65 and treated in European region were raised. In answer to questions, the applicant presented the baseline data and discussed the age subgroups. Except for slightly higher ApoE4 homozygous gene (23.5% in lecanemab group) and higher tau load (2.02) in the <65 years group, the baseline characteristics look similar between age groups.

Finally, an evaluation of the magnitude of effect has to be made in the context of the characterisation (or lack thereof) of the effect as slowing of disease progression or as disease-modifying (see the EMA Guidelines on Alzheimer's disease for definitions). This would help understand how the clinical effect would evolve over time. The delayed-start data provided is limited and the applicant has not demonstrated that a slowing down of disease progression is shown. From a visual inspection, it is

observed that the worsening observed before Month 18 in patients treated with lecanemab seems continue on a close trajectory, and that the difference, especially for ADAS-Cog14, appears to shrink.

The applicant has not demonstrated the robustness of the exercise of comparison with the ADNI cohort. Because the natural history cohort and the placebo treatment arm show comparable trajectories in the first 18 months, the applicant argues that the later part of the natural history cohort can be used to imply an increased separation of lecanemab and placebo groups beyond Month 18. Although the matching of the ADNI population may have helped reduce bias, the non-randomised nature of these comparisons has inherent limitations, and unexplained biases are expected to remain. It is therefore not possible to infer further separation between lecanemab and a hypothetical placebo arm based on the natural history cohort.

Overall, the concerns about long-term efficacy together with the poor correlation between brain amyloid load and clinical endpoints did not allow to support the demonstration of disease modifying properties. In the answer to questions, the applicant agreed to remove any disease modifying or slowing of disease-progression claim. Nonetheless, the absence of demonstration of disease-modifying properties has a bearing on the appraisal of the efficacy profile, and hence on the benefit-risk evaluation.

2.6.7. Conclusions on the clinical efficacy

Overall, the efficacy results are coming from a single pivotal Phase 3 study. The effect size in the primary analysis (-0.451 in change from baseline in CDR-SB at 18 months) is considered small. An even smaller effect is seen in the ApoE4 homozygous population. There are also concerns regarding the lack of relationship between the pharmacodynamics and the clinical outcomes, and on lack of data on the maintenance of effect in the longer term. This view is supported by the SAG Neurology experts who considered by consensus that the above-mentioned observed differences in favour of Leqembi are n*ot clinically relevant and meaningful for the patients*.

2.6.8. Clinical safety

Table 33. Overview of lecanemab clinical studies

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
Phase 3 and 2: Studies in Subjects With EAD					
BAN2401-G000-301 Core (Study 301 Core) Total sites: 235 Sites in: North America (112), Europe (which includes Australia) (55), Asia-Pacific (47), and China (21)	27 Mar 2019 to 25 Aug 2022	Double-blind, parallel-group, PBO-controlled, multicenter study to confirm the safety and efficacy of lecanemab in subjects with EAD (MCI) due to AD with intermediate likelihood/prodromal AD or mild AD dementia) and confirmed amyloid pathology indicated by positive amyloid load	Male and female subjects 50 to 90 years, inclusive MCI due to AD intermediate likelihood and mild AD dementia MMSE score ≥22 & ≤30 at Screening and Baseline Positive biomarker for brain amyloid pathology as indicated by 1 of the following: • PET assessment of imaging agent uptake into brain CSF assessment of t-tau/Aβ[1-42]	PBO (IV) LEC10-BW (IV)	PBO Randomized/completed: 897/757 Sex: 421M, 476F Race: 696W, 150A, 25B, 12O, 12MI, 2NAM, 0NH *APOE4* carrier: 611Y (133HO, 478HET), 286N Clinical Subgroup: 555MCI, 342Mild AD LEC10-BW Randomized/completed: 898/729 Sex: 436M, 462F Race: 685W, 153A, 22B, 21O, 16MI, 0NAM, 1NH *APOE4* carrier: 620Y (141HO, 479HET), 278N Clinical Subgroup: 552MCI, 346Mild AD

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
BAN2401-G000-301 Open-label extension (Study 301 OLE Phase) Total sites: 184 Sites in: North America (97), Asia-Pacific (45), Europe (which includes Australia) (42), and China (0)	10 Nov 2020 to ongoing	OLE Phase to Study 301	Subjects who have completed the Core Study	LEC10-BW (IV) (or 720 mg SC as a weekly dose in optional substudy; SC data not included in this submission)	LEC10-BW Enrolled/completed: 964/0 Sex: 467M, 497F Race: 720W, 192A, 26B, 13O, 12MI, 1NAM *APOE4* carrier: 600Y (126HO, 474HET), 364N Clinical Subgroup: 627MCI, 337Mild AD
BAN2401-G000-201 Core (Study 201 Core) Total sites: 149 sites in North America (93), Europe (34), and Asia-Pacific (22)	20 Dec 2012 to 19 Jul 2018 (21-month data; Core Study)	Double–blind, parallel-group, PBO-controlled, multicenter and global study utilized a dose-finding RAR design to evaluate the safety, tolerability, and efficacy of lecanemab in subjects with MCI due to AD – intermediate likelihood, or with mild AD dementia (collectively designated as EAD)	Male and female subjects 50 to 90 years, inclusive MCI due to AD and mild AD. MMSE score ≥22 & ≤30 at Screening and Baseline, except for, DE, ES, FR, NL SE, and the UK, where the score had to be ≥22 and ≤28 at Screening and Baseline Positive amyloid load as indicated by 1 of the following: • PET assessment of imaging agent uptake into brain • CSF assessment of Aβ (1-42)	PBO (IV) LEC2.5-BW (IV) LEC5-M (IV) LEC5-BW (IV) LEC10-M (IV) LEC10-BW (IV)	PBO Randomized/completed: 247/177 Sex: 107M/138F Race: 222W, 5B, 10JP, 6OA, 1CN, 1O *APOE4* carrier: 174Y (40HO, 134HET), 71N Clinical Subgroup: 159MCI, 86Mild AD
					LEC2.5-BW Randomized/completed: 52/35 Sex: 26M/26F Race: 48W, 2B, 1JP, 1OA *APOE4* carrier: 38Y (5HO, 33HET), 14N Clinical Subgroup: 34MCI, 18Mild AD

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
					LEC5-M Randomized/completed: 51/37 Sex: 25M/26F Race: 49W, 1B, 1OA *APOE4* carrier: 40Y (12HO, 28 HET), 11N Clinical Subgroup: 36MCI, 15Mild AD
					LEC5-BW Randomized/completed: 92/61 Sex: 42M/50F Race: 76W, 4B, 6JP, 3OA, 3O *APOE4* carrier: 84Y (14HO, 70HET), 8N Clinical Subgroup: 53MCI, 39Mild AD
					LEC10-M Randomized/completed: 253/155 Sex: 141M/112F Race: 228W, 5B, 12JP, 5OA, 3O *APOE4* carrier: 225Y (60HO, 165HET), 28N Clinical Subgroup: 170MCI, 83Mild AD

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
					LEC10-BW Randomized/completed: 161/87 Sex: 91M/70F Race: 150W, 4B, 5JP, 2OA *APOE4* carrier: 49Y (10HO, 39HET), 112N Clinical Subgroup: 95MCI, 66Mild AD
BAN2401-G000-201 Open-label extension (Study 201 OLE Phase) Total sites: 59 sites in North America (40), Europe (5), and Asia-Pacific (14)	12 Dec 2018 to ongoing	OLE Phase to Study 201	Completed Visit 42 (Week 79) of the Core Study or who discontinued study drug during the Core due to select reasons	LEC10-BW (IV)	LEC10-BW Enrolled/completed: 180/0 Sex: 93M/87F Race: 148W, 2B, 30A (including 21JP, 1CN, 8SK) *APOE4* carrier: 125Y (28HO, 97HET), 55N Clinical Subgroup at the start of Core: 110MCI, 70Mild AD

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
Phase 3: Subjects With Preclinical AD					
BAN2401-G000-303 (Study 303) Total sites: 102 Sites in: US (70), Japan (13), Australia (6), Spain (5), Canada (3), United Kingdom (4), and Singapore (1)	14 Jul 2020 to ongoing	Study 303 consists of 2 trials (A45 and A3) under a single protocol and is a double-blind, parallel-treatment arm, PBO-controlled study to evaluate efficacy and safety of treatment with lecanemab in subjects with preclinical AD and elevated amyloid (A45 Trial) and subjects with early preclinical AD and intermediate amyloid (A3 Trial)	Male or female subjects 55 to 80 years, inclusive Known before Screening to have elevated brain amyloid according to previous PET or CSF testing A45 Preclinical AD with elevated amyloid MMSE score ≥27 Global CDR score of 0 A3 Early preclinical AD with intermediate amyloid MMSE score ≥27 at Screening Global CDR score of 0 at Screening	A45 PBO (IV) or LEC5-BW (IV) through 8 weeks (titration), then LEC10-BW (IV) through 96 weeks (induction), then LEC10-M (IV) through 216 weeks (maintenance) A3 PBO (IV), or LEC5-M (IV) through 8 weeks (titration), then LEC10-M (IV) through 216 weeks	Randomized: 322 subjects had been randomized (223 subjects in the A45 Trial, and 99 subjects in the A3 Trial). Demographics not available.

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
Phase 2/3 Study in Subjects With Dominantly-Inherited AD					
DIAN-TU-001 (ongoing)	22 Dec 2021 to ongoing	Randomized, double-blind, PBO-controlled platform trial of potential disease modifying therapies utilizing biomarker, cognitive, and clinical endpoints in dominantly inherited Alzheimer's disease	Male or female subjects 18 to 80 years, inclusive. -10 to +10 EYO (secondary prevention population): within - 10 to +10 estimated age at symptom onset, CDR 0 to 1, known eligible mutation carrier or at 50% risk −25 to −11 EYO (primary prevention population): within 11 to 25 years younger than their estimated age at symptom onset, CDR 0, known carrier or mutation in their family pedigree.	E2814 (IV) 1500 mg every 4 weeks, or LEC10-BW (IV) through 48 to 80 months depending on time required for full recruitment.	No data to report

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
Phase 1: Subjects With AD and Healthy Subjects					
BAN2401-A001-101 (Study 101) Total sites: 15 US: 15	31 Aug 2010 to 13 Sep 2012	Double-blind, randomized, PBO-controlled study in subjects with mild to moderate AD. This study comprised 2 parts: 1) a SAD part evaluating doses of 0.1, 0.3, 1, 3, 10, and 15 mg/kg and 2) a MAD part evaluating doses of 0.3, 1, and 3 mg/kg (dosing every 4 weeks), and a dose of 10 mg/kg (dosing biweekly). The MAD part of the study was initiated after completion of the 1 mg/kg dose in the SAD part	Male and female subjects age ≥50 years. Mild to moderate AD. MMSE 16 to 28, inclusive. First 2 SAD cohorts MMSE >22 at Screening	SAD 0.1 mg/kg (SAD1) 0.3 mg/kg (SAD2) 1 mg/kg (SAD3) 3 mg/kg (SAD4) 10 mg/kg (SAD5) 15 mg/kg (SAD6) MAD 0.3 mg/kg (MAD1) 1 mg/kg (MAD2) 3 mg/kg (MAD3) 10 mg/kg (MAD4)	SAD Randomized/completed: 36/35 PBO Randomized/completed: 12/11 Sex: 7M/5F Race: 10W, 1B, 1A *APOE4* carrier: 5Y, 7N LEC0.1 Randomized/completed: 6/5 Sex: 2M/4F Race: 5W, 1B *APOE4* carrier: 2Y, 4N LEC0.3 Randomized/completed: 6/6 Sex: 4M/2F Race: 4W, 1B, 1A *APOE4* carrier: 4Y, 1N, 1UNK LEC1 Randomized/completed: 6/6 Sex: 4M/2F Race: 6W *APOE4* carrier: 2Y, 3N, 1UNK

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
				SAD PBO (IV) LEC0.1 (IV) LEC0.3 (IV) LEC1 (IV) LEC3 (IV) LEC10 (IV) LEC15 (IV)	LEC3 Randomized/completed: 6/6 Sex: 3M/3F Race: 3W, 3B *APOE4* carrier: 3Y, 3N
					LEC10 Randomized/completed: 6/6 Sex: 4M/ 2F Race: 6W *APOE4* carrier: 4Y, 2N
					LEC15 Randomized/completed: 6/6 Sex: 1M/5F Race: 4W, 2B *APOE4* carrier: 3Y, 2N, 1UNK
				MAD PBO (IV) LEC0.3-M (IV) LEC1-M (IV) LEC3-M (IV) LEC10-14D (IV)	MAD Study PBO Randomized/completed: 8/8 Sex: 6M/2F Race: 6W, 1B, 1O *APOE4* carrier: 4Y, 3N, 1UNK
					LEC0.3-M Randomized/completed: 6/5 Sex: 4M/2F Race: 4W, 1B, 1O *APOE4* carrier: 5Y, 1N

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
				MAD PBO (IV) LEC0.3-M (IV) LEC1-M (IV) LEC3-M (IV) LEC10-14D (IV)	LEC1-M Randomized/completed: 6/4 Sex: 1M/5F Race: 4W, 2B *APOE4* carrier: 5Y, 1N
					LEC3-M Randomized/completed: 6/5 Sex: 2M/4F Race: 5W, 1B *APOE4* carrier: 3Y, 3N
					LEC10-14D Randomized/completed: 6/6 Sex: 4M/2F Race: 5W, 1B *APOE4* carrier: 2Y, 4N
BAN2401-J081-104 (Study 104) Total sites: 7 JP: 7	20 Sep 2013 to 26 Mar 2015	Randomized, double-blind, PBO-controlled, multicenter multiple ascending dose study in subjects with MCI due to AD and mild AD	Male or female subjects 50 to 90 years, inclusive. MCI due to AD and mild AD. MMSE score ≥22 & ≤30. CDR of 0.5 or 1.0 and a memory box score of 0.5 or greater at Screening. Positive amyloid load as indicated by PET assessment of imaging agent uptake into brain (Cohort 2 and Cohort 3)	PBO (IV) LEC2.5 (IV) LEC5 (IV) LEC10 (IV) Second dose 6 weeks after first, then every 2 weeks x 4	PBO Randomized/completed: 7/5 Sex: 1M/4F Race: 5JP *APOE4* carrier: 3Y, 2N
					LEC2.5 Randomized/completed: 6/6 Sex: 4M/2F Race: 6 JP *APOE4* carrier: 4Y, 2N

Study Number No. of Sites: Countries	Study Dates	Study Design/Population	Diagnosis, Main Inclusion Criteria	Study Treatments (Route of Administration)	No. Subjects by Arm Randomized/Completed[a] Sex Race *APOE4* Carrier Status Clinical Subgroup[b]
				PBO (IV) LEC2.5 (IV) LEC5 (IV) LEC10 (IV) Second dose 6 weeks after first, then every 2 weeks x 4	LEC5 Randomized/completed: 6/6 Sex: 3M/3F Race: 6 JP *APOE4* carrier: 5Y, 1N
					LEC10 Subjects randomized/completed: 7/7 Sex: 5M/2F Race: 7JP *APOE4* carrier: 4Y, 3N
BAN2401-A001-004 (Study 004) Total sites: 1 US: 1	07 Sep 2021 to 07 Dec 2021	Open-label, parallel-group, single site; randomized study to evaluate the absolute bioavailability of single dose SC administration of lecanemab in healthy volunteers	Male or female healthy subjects ≥18 to ≤65 years old. Non-Japanese Japanese subjects assigned to SC treatment (age ≥20 years): born in Japan, of Japanese parents and grandparents, living no more than 5 years outside of Japan	LEC10 (IV) LEC 700 (SC)	LEC10 (IV) Randomized/completed: 30/30 Sex: 20M/10F Race: 17W, 8B, 5A
					LEC 700 (SC) Randomized/completed: 30/29 Sex: 18M/11F Race: 16W, 9A, 4B
BAN2401-A001-005 (Study 005) Total sites: 1 US: 1	06 Sep 22 - ongoing	Open-label, parallel-group, single site; randomized study to evaluate the bioequivalence of single dose SC formulation of lecanemab supplied in vials and a single use AI in healthy volunteers	Male or female healthy subjects ≥18 to ≤65 years old	LEC 720 (SC) vial LEC 720 (SC) vial AI	No data to report

Four additional subjects that were randomized to PBO (2 in BAN2401-J081-104 and 2 in BAN2401-G000-201) dropped out before the start of treatment.
A = Asian, Ab = amyloid beta; AD = Alzheimer's disease, APOE4 = apolipoprotein E4, AI = autoinjector, B = Black, CDR = Clinical Dementia Rating; CN = Chinese; CSF = cerebrospinal fluid, CSR = clinical study report; EAD = early Alzheimer's disease, EYO = Estimated years from symptom onset, F = female, HET = heterozygous, HO = homozygous, ISS = Integrated Summary of Safety; JP = Japanese, LEC = lecanemab; M = male, MAD = multiple ascending dose, MCI = mild cognitive impairment, MI = missing, MU = multiple, NAM = American Indian or Alaskan Native, NH = Native Hawaiian or Other Pacific Islander, O = other, OA = other Asian, IV = intravenous, MMSE = Mini Mental State Examination, N = no, OLE = open-label extension, PBO = PBO, PET = positron emission tomography, RAR = response adaptive randomisation; SAD = single ascending dose, SC = subcutaneous, sCSR = synoptic clinical study report, t-tau =total tau, UNK = unknown, US = United States, W = White (or Caucasian), Y = yes. a: Randomized set. b: Provided as available

The safety data presented by the applicant is mainly from a single randomized phase 3 study and a supportive phase 2 study in patients with early Alzheimer's disease (MCI due to AD and mild AD dementia) which is the intended population. In addition, two analysis pools were presented (Pool Core, the pooled data from the phase 2 and the pivotal phase 3, and Pool LEC10-BW, which includes all patients who received lecanemab at the intended dose of (n=1694) in the Core or OLE Phase of Studies 301 and 201).

2.6.8.1. Patient exposure

BAN2401-G000-301

Table 34. Cumulative extent of exposure - study 301 core study (safety analysis set)

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

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

In **Study 301 OLE** Phase (LEC10-BW Treated Period, DCO dec 2022) the mean duration of exposure to LEC10-BW (n=1612) is 14.06 months, with 1007 subjects exposed to LEC10-BW for at least 12 months and 221 subjects exposed to LEC10-BW for at least 24 months.

In **study 201 Core**, the rate of patients who received LEC10 BW ≥ 12 months (97/161 patients, 60.2%) was lower than in placebo arm (202/245 patients, 82.4%). Similarly, the number of patients who received LEC10 BW ≥ 18 months (76/161 patients, 60.2%) was lower than in placebo arm (157/245 patients, 82.4%). The justification of the applicant that discontinuation of *APOE4* patients who received lecanemab for less than 6 months is also likely to have impacted extent of exposure is acknowledged.

In **Study 201 OLE,** Phase the mean duration of exposure to LEC10-BW for the 180 subjects is 30.13 months, with 149 subjects exposed to LEC10-BW for at least 12 months and 124 subjects exposed to LEC10-BW for at least 24 months

In the **Pool core**, the addition of data from study 301 to study 201 in LEC10 BW group, tend to reduce the gap with placebo group with a mean (SD) duration of exposure of 16.31 (4.21) in placebo group and 15.19 (5.59) months in LEC10 BW group.

Pool LEC10-BW

Table 35. Cumulative extent of exposure - pool LEC10-BW (safety analysis set) - DCO April 2022

Duration of Exposure	Lecanemab 10 mg/kg Biweekly (N=1694) n (%)
Duration (months)[a], n (%)	
≥6 weeks	1578 (93.2)
≥3 months	1425 (84.1)
≥6 months	1268 (74.9)
≥9 months	1112 (65.6)
≥12 months	1014 (59.9)
≥15 months	960 (56.7)
≥18 months	828 (48.9)
≥21 months	498 (29.4)
≥24 months	378 (22.3)
≥27 months	250 (14.8)
≥30 months	170 (10.0)
Duration (months)	
n	1694
Mean (SD)	16.49 (12.472)
Median	17.90
Min, Max	0.5, 57.9
Total duration (subject-years)[b]	2327.39

Max = maximum, Min = minimum, N = number of subjects in treatment group, n = number of subjects at each visit. a: Duration (months) = ([date of last dose – date of first dose +1]/ 7 + 1 treatment cycle)/ 52*12. b: Number of subject-years = summation over all subjects' exposure durations

Table 36. Cumulative extent of exposure - pool LEC10-BW (safety analysis set)-DCO Dec 2022

Overall

Duration of Exposure	Lecanemab 10 mg/kg Biweekly (N=1915) n (%)
Duration (months)[a], n(%)	
>=6 weeks	1841 (96.1)
>=3 months	1743 (91.0)
>=6 months	1564 (81.7)
>=9 months	1380 (72.1)
>=12 months	1238 (64.6)
>=15 months	1092 (57.0)
>=18 months	959 (50.1)
>=21 months	823 (43.0)
>=24 months	662 (34.6)
>=27 months	515 (26.9)
>=30 months	397 (20.7)
Duration (months)	
n	1915
Mean (SD)	19.36 (13.825)
Median	18.00
Min, Max	0.5, 67.4
Total duration (subject-years)[b]	3089.90

2.6.8.2. Adverse events

Table 37. Overview of treatment-emergent adverse events - study 301 core (safety analysis set)

Category	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
TEAEs	735 (81.9)	798 (88.9)
Treatment-related TEAEs[a]	197 (22.0)	401 (44.7)
Severe TEAEs	61 (6.8)	67 (7.5)
Serious TEAEs	101 (11.3)	126 (14.0)
Deaths[b]	7 (0.8)	6 (0.7)
Other SAEs[c]	94 (10.5)	120 (13.4)
Life threatening	2 (0.2)	5 (0.6)
Requires inpatient hospitalization or prolongation of existing hospitalization	86 (9.6)	106 (11.8)
Persistent or significant disability or incapacity	1 (0.1)	4 (0.4)
Congenital anomaly/birth defect	0	0
Important medical events	14 (1.6)	18 (2.0)
TEAEs leading to study drug dose adjustment	93 (10.4)	218 (24.3)
TEAEs leading to study drug withdrawal	26 (2.9)	62 (6.9)
TEAEs leading to study drug dose interruption	71 (7.9)	175 (19.5)
TEAEs leading to infusion interruption	11 (1.2)	22 (2.4)
TEAEs of special interest	156 (17.4)	379 (42.2)

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

For each row category, a subject with 2 or more AEs in that category was counted only once. MedDRA Version 25.0 AE = adverse event, MedDRA = medical Dictionary for Regulatory Activities, LEC10-BW = lecanemab 10 mg biweekly, PBO = placebo, SAE = serious adverse event, TEAE = treatment-emergent adverse event. a: Included TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality. b: Included all subjects with SAE resulting in death. c: Included subjects with nonfatal SAEs only. If a subject had both fatal and nonfatal SAEs, the subject was counted in the previous fatal row and was not counted in the nonfatal row.

Table 38. Treatment-emergent adverse events with incidence in at least 5% of subjects in any treatment group by decreasing frequency - study 301 core (safety analysis set)

MedDRA Preferred Term	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
Subjects with any TEAE	735 (81.9)	798 (88.9)
Infusion-related reaction	64 (7.1)	236 (26.3)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	69 (7.7)	126 (14.0)
Amyloid related imaging abnormality-oedema/effusion	15 (1.7)	113 (12.6)
Headache	73 (8.1)	100 (11.1)
Fall	86 (9.6)	93 (10.4)
Urinary tract infection	82 (9.1)	78 (8.7)
COVID-19	60 (6.7)	64 (7.1)
Back pain	52 (5.8)	60 (6.7)
Arthralgia	62 (6.9)	53 (5.9)
Superficial siderosis of central nervous system	22 (2.5)	50 (5.6)
Dizziness	46 (5.1)	49 (5.5)
Diarrhoea	58 (6.5)	48 (5.3)
Anxiety	38 (4.2)	45 (5.0)

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subject with two or more AEs with the same preferred term was counted only once for that preferred term. Cerebral microhaemorrhages included those deemed not ARIA-H by investigator. TEAEs were ordered by decreasing frequency in 10 mg/kg Biweekly group, then placebo group. MedDRA Version 25.0. AE = adverse event, ARAI-H = amyloid-related imaging abnormality- microhaemorrhage and hemosiderin deposit, COVID-19 = Coronavirus disease of 2019, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in treatment group, n = number of subjects at each visit, PBO = placebo, TEAE = treatment-emergent adverse event.

Table 39. Treatment-emergent adverse events by decreasing frequency - study 301 core (safety analysis set)

MedDRA Preferred Term	Placebo (N = 897) n(%)	Lecanemab 10 mg/kg Biweekly (N = 898) n(%)
Subjects with any TEAE	735 (81.9)	798 (88.9)
Hypertension	43 (4.8)	41 (4.6)

MedDRA Preferred Term	Placebo (N = 897) n(%)	Lecanemab 10 mg/kg Biweekly (N = 898) n(%)
Contusion	39 (4.3)	38 (4.2)
Fatigue	24 (2.7)	37 (4.1)
Nasopharyngitis	35 (3.9)	36 (4.0)
Pain in extremity	34 (3.8)	32 (3.6)
Nausea	25 (2.8)	31 (3.5)
Vomiting	22 (2.5)	29 (3.2)
Rash	17 (1.9)	29 (3.2)
Upper respiratory tract infection	19 (2.1)	25 (2.8)
Insomnia	21 (2.3)	24 (2.7)
Pyrexia	18 (2.0)	24 (2.7)
Atrial fibrillation	14 (1.6)	24 (2.7)
Depression	38 (4.2)	23 (2.6)
Skin laceration	22 (2.5)	23 (2.6)
Haematuria	7 (0.8)	21 (2.3)
Cough	17 (1.9)	20 (2.2)

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Table 14.3.1.3.2.1
Treatment-Emergent Adverse Events With Incidence >=2% of Subjects in Any Treatment Group by Decreasing Frequency
Core Study
Safety Analysis Set

MedDRA Preferred Term	Placebo (N = 897) n(%)	Lecanemab 10 mg/kg Biweekly (N = 898) n(%)
Constipation	22 (2.5)	19 (2.1)
Osteoarthritis	14 (1.6)	18 (2.0)
Syncope	12 (1.3)	18 (2.0)
Anaemia	18 (2.0)	7 (0.8)

In the TEAEs list of SOC terms, more cardiac events occurred in the LEC10 BW arm than in placebo (9.5% vs 6.8%) Parts of this is explained by atrial fibrillation 1.6% vs 2.7%, but also atrioventricular block first degree (0.4 vs 0.9%), bundle branch block left (0.3 vs 0.9%), sinus bradycardia (0.3 vs 0.8%) and angina pectoris (0.3% vs 1%) occurred more often in the LEC10 BW.

In study 201, the incidence of TEAE was similar in placebo (87.3%) and LEC10 BW arms (85.7%) with no obvious dose-effect across increasing doses of lecanemab and severe TEAEs had similar incidence between placebo (8.2%) and LEC10 BW (9.9%). While no dose-effect seem to be evidenced, lower incidence of severe TEAEs were observed in groups with a monthly administration (LEC5 M and LEC10 M).

Table 40. Overview of treatment-emergent adverse events - study 201 core (safety analysis set)

Category	Placebo (N=245) n (%)	Lecanemab 2.5 mg/kg Biweekly (N=52) n (%)	Lecanemab 5 mg/kg Monthly (N=51) n (%)	Lecanemab 5 mg/kg Biweekly (N=92) n (%)	Lecanemab 10 mg/kg Monthly (N=253) n (%)	Lecanemab 10 mg/kg Biweekly (N=161) n (%)
TEAEs	214 (87.3)	46 (88.5)	47 (92.2)	80 (87.0)	237 (93.7)	138 (85.7)
Treatment-related TEAEs	64 (26.1)	23 (44.2)	25 (49.0)	31 (33.7)	135 (53.4)	76 (47.2)
Severe TEAEs	20 (8.2)	7 (13.5)	2 (3.9)	12 (13.0)	17 (6.7)	16 (9.9)
Serious TEAEs	42 (17.1)	8 (15.4)	4 (7.8)	16 (17.4)	29 (11.5)	21 (13.0)
Deaths[a]	2 (0.8)	2 (3.8)	0	1 (1.1)	1 (0.4)	0
Other SAEs[b]	40 (16.3)	6 (11.5)	4 (7.8)	15 (16.3)	28 (11.1)	21 (13.0)
Life threatening	0	1 (1.9)	0	0	3 (1.2)	0
Requires inpatient hospitalization or prolongation of existing hospitalization	39 (15.9)	6 (11.5)	4 (7.8)	14 (15.2)	24 (9.5)	20 (12.4)
Persistent or significant disability or incapacity	0	0	0	0	0	0
Congenital anomaly / birth defect	0	0	0	0	0	0
Important medical events	5 (2.0)	0	0	2 (2.2)	5 (2.0)	2 (1.2)
TEAEs leading to study drug dose adjustment	48 (19.6)	14 (26.9)	8 (15.7)	24 (26.1)	65 (25.7)	42 (26.1)
TEAEs leading to study drug withdrawal	14 (5.7)	7 (13.5)	4 (7.8)	10 (10.9)	47 (18.6)	24 (14.9)
TEAEs leading to study drug dose reduction	0	0	0	0	0	0
TEAEs leading to study drug dose interruption	36 (14.7)	8 (15.4)	5 (9.8)	15 (16.3)	20 (7.9)	19 (11.8)
TEAEs leading to infusion interruption	6 (2.4)	3 (5.8)	2 (3.9)	5 (5.4)	4 (1.6)	2 (1.2)
TEAEs of special interest	21 (8.6)	7 (13.5)	10 (19.6)	26 (28.3)	88 (34.8)	53 (32.9)

A TEAE is defined as an AE that: emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline); or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment; or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. For each row category, a subject with 2 or more adverse events in that category was counted only once. MedDRA Version 25.0. AE = adverse events, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse events, TEAE = treatment-emergent adverse event. a: Includes all subjects with SAE resulting in death. b: Includes subjects with nonfatal SAEs only. If a subject had both fatal and nonfatal SAEs, the subject was counted in the previous row ("Death") and was not counted in this row.

Table 41. Treatment-emergent adverse events by preferred term and decreasing frequency – incidence ≥5% in highest dose group - study 201 core (safety analysis set)

MedDRA Preferred Term	Placebo (N=245) n (%)	Lecanemab 2.5 mg/kg Biweekly (N=52) n (%)	Lecanemab 5 mg/kg Monthly (N=51) n (%)	Lecanemab 5 mg/kg Biweekly (N=92) n (%)	Lecanemab 10 mg/kg Monthly (N=253) n (%)	Lecanemab 10 mg/kg Biweekly (N=161) n (%)
Subjects with any TEAE	214(87.3)	46 (88.5)	47 (92.2)	80 (87.0)	237 (93.7)	138 (85.7)
Infusion-related reaction	8 (3.3)	3 (5.8)	4 (7.8)	11 (12.0)	59 (23.3)	32 (19.9)
Headache	25 (10.2)	8 (15.4)	4 (7.8)	17 (18.5)	41 (16.2)	22 (13.7)
Urinary tract infection	32 (13.1)	5 (9.6)	5 (9.8)	17 (18.5)	24 (9.5)	17 (10.6)
Upper respiratory tract infection	40 (16.3)	7 (13.5)	7 (13.7)	10 (10.9)	23 (9.1)	17 (10.6)
Amyloid related imaging abnormality-oedema/effusion	2 (0.8)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)
Fall	32 (13.1)	3 (5.8)	6 (11.8)	13 (14.1)	21 (8.3)	15 (9.3)
Cough	12 (4.9)	1 (1.9)	2 (3.9)	4 (4.3)	11 (4.3)	14 (8.7)
Nasopharyngitis	28 (11.4)	3 (5.8)	7 (13.7)	9 (9.8)	18 (7.1)	13 (8.1)
Diarrhoea	12 (4.9)	5 (9.6)	7 (13.7)	12 (13.0)	16 (6.3)	13 (8.1)
Dizziness	18 (7.3)	4 (7.7)	0	10 (10.9)	9 (3.6)	12 (7.5)
Back pain	24 (9.8)	4 (7.7)	6 (11.8)	4 (4.3)	18 (7.1)	11 (6.8)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	11 (4.5)	2 (3.8)	7 (13.7)	10 (10.9)	18 (7.1)	9 (5.6)
Fatigue	15 (6.1)	4 (7.7)	1 (2.0)	7 (7.6)	17 (6.7)	8 (5.0)
Arthralgia	19 (7.8)	0	4 (7.8)	7 (7.6)	14 (5.5)	7 (4.3)
Contusion	7 (2.9)	2 (3.8)	5 (9.8)	6 (6.5)	11 (4.3)	7 (4.3)
Hypertension	13 (5.3)	1 (1.9)	1 (2.0)	3 (3.3)	10 (4.0)	7 (4.3)
Nausea	10 (4.1)	1 (1.9)	4 (7.8)	8 (8.7)	14 (5.5)	6 (3.7)
Anxiety	14 (5.7)	1 (1.9)	3 (5.9)	3 (3.3)	10 (4.0)	6 (3.7)
Sinusitis	8 (3.3)	1 (1.9)	5 (9.8)	1 (1.1)	9 (3.6)	6 (3.7)
Depression	13 (5.3)	1 (1.9)	3 (5.9)	6 (6.5)	12 (4.7)	5 (3.1)

A TEAE was defined as an AE that: emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline); or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment; or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subject with 2 or more AEs in the same preferred term was counted only once for that preferred term.

Cerebral microhaemorrhages included those deemed not ARIA-H by investigator. TEAE were ordered by decreasing frequency in 10 mg/kg biweekly, 10 mg/kg monthly, 5 mg/kg biweekly, 5 mg/kg monthly and 2.5 mg/kg biweekly groups sequentially (e.g., by 10 mg/kg biweekly first, then 10 mg/kg monthly if tied for 10 mg/kg biweekly). MedDRA Version 25.0. AE = adverse events, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event

The most frequent severe treatment-related TEAEs (in 2 or more subjects in any treatment group) were as follows:

- Lecanemab 10 mg/kg monthly (N=253): ARIA–E (2 [<1.0%] subjects).
- Lecanemab 10 mg/kg biweekly (N=161): ARIA–E (3 [1.9%] subjects); cerebral microhaemorrhage (2 [1.2%] subjects).
- Lecanemab treatment groups overall (N=609): ARIA–E (5 [<1.0%] subjects); cerebral microhaemorrhage and transient ischaemic attack (each 2 [<1.0%] subjects).

In **Pool Core** and **Pool LEC10 BW**, results were overall consistent with study 301

2.6.8.3. Serious adverse events, deaths, and other significant events

Deaths

Table 42. Treatment-emergent adverse events leading to death by system organ class and preferred term - study 301 core (safety analysis set)

MedDRA System Organ Class Preferred Term	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
Subjects with any TEAE leading to death	7 (0.8)	6 (0.7)
Cardiac disorders	1 (0.1)	1 (0.1)
Myocardial infarction	1 (0.1)	1 (0.1)
General disorders and administration site conditions	1 (0.1)	1 (0.1)
Death	1 (0.1)	1 (0.1)
Infections and infestations	1 (0.1)	1 (0.1)
COVID-19	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2)	1 (0.1)
Metastases to bone	1 (0.1)	0
Metastases to meninges	0	1 (0.1)
Pancreatic carcinoma	1 (0.1)	0
Nervous system disorders	1 (0.1)	1 (0.1)
Cerebrovascular accident	0	1 (0.1)
Haemorrhage intracranial	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1 (0.1)
Acute respiratory failure	1 (0.1)	0
Respiratory failure	0	1 (0.1)

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subject

with 2 or more AEs in the same system organ class (or with the same preferred term) was counted only once for that system organ class (or preferred term). Cerebral microhaemorrhages included those deemed not ARIA-H by investigator. MedDRA Version 25.0.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in treatment group, n = number of subjects at each visit, TEAE = treatment-emergent adverse event.

In **Core study 201**, there was 2 treatment emergent deaths in placebo arm (acute respiratory failure and sarcoma) and 4 deaths in lecanemab arms (brain neoplasm, cardiac arrest, multiple organ dysfunction and spinal cord injury). There were 2 additional deaths during OLE in lecanemab arms, 1 patient died due to a cervical vertebral fracture and one patient died of a neuroendocrine carcinoma.

No death appears to be related to a cerebral haemorrhagic event before data cut-off.

In **Pool Core**, deaths were consistent with data of both Study Core 201 and 301.

In addition, the applicant reported 2 publicized cases of deaths in the Study 301 OLE Phase that occurred after the data cutoff (15 Apr 2022) (both macrohaemorrhage events). At the DCO Dec 2022, 6 additional deaths were reported, of which 4 were considered at least possibly related to study treatment and 3/4 fatal events occurred in patients with concurrent risk factors (i.e. CAA, anticoagulant or thrombolytic treatment).

Serious adverse events

In **study 301**, the most commonly reported TESAEs (at least 2% in LEC10-BW and greater than PBO) were: cardiac disorders (PBO 1.0%; LEC10-BW 2.1%), infections and infestations (PBO 1.0%; LEC10-BW 2.1%), SOCs of nervous system disorders (PBO 1.7%; LEC10-BW 3.3%) and injury, poisoning and procedural complications (PBO 2.1%; LEC10-BW 3.5%).

The incidence of treatment-related, TESAEs were lower in PBO (0.6%) than LEC10-BW (2.7%). Most events were reported by single subjects in either group apart from infusion-related reactions (1.2%), ARIA-E (0.8%), ARIA-H (0.2%), and cerebral haemorrhage (0.2%), which were only reported in LEC10-BW.

Table 43. Treatment-emergent serious adverse events occurring in ≥2 subjects by decreasing frequency - study 301 core (safety analysis set)

MedDRA Preferred Term	Placebo (N = 897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)
Subjects with any treatment-emergent SAE	101 (11.3)	126 (14.0)
Infusion-related reaction	0	11 (1.2)
Amyloid related imaging abnormality-oedema/effusion	0	7 (0.8)
Atrial fibrillation	3 (0.3)	6 (0.7)
Syncope	1 (0.1)	6 (0.7)
Angina pectoris	0	6 (0.7)
Diverticulitis	1 (0.1)	4 (0.4)
Non-cardiac chest pain	0	4 (0.4)
Pneumonia	3 (0.3)	3 (0.3)
Subdural haematoma	3 (0.3)	3 (0.3)
Hip fracture	2 (0.2)	3 (0.3)
Inguinal hernia	2 (0.2)	3 (0.3)
Transient ischaemic attack	2 (0.2)	3 (0.3)
Fall	1 (0.1)	3 (0.3)
Cerebral haemorrhage	0	3 (0.3)
Acute respiratory failure	3 (0.3)	2 (0.2)
Osteoarthritis	3 (0.3)	2 (0.2)
COVID-19	2 (0.2)	2 (0.2)
Dehydration	2 (0.2)	2 (0.2)
Cerebrovascular accident	1 (0.1)	2 (0.2)
Femoral neck fracture	1 (0.1)	2 (0.2)
Acute kidney injury	0	2 (0.2)
Acute myocardial infarction	0	2 (0.2)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	0	2 (0.2)
COVID-19 pneumonia	0	2 (0.2)
Cellulitis	0	2 (0.2)
Coronary artery disease	0	2 (0.2)
Diarrhoea	0	2 (0.2)
Hyponatraemia	0	2 (0.2)
Invasive ductal breast carcinoma	0	2 (0.2)
Pulmonary oedema	0	2 (0.2)
Respiratory failure	0	2 (0.2)
Thoracic vertebral fracture	0	2 (0.2)
Ankle fracture	3 (0.3)	1 (0.1)
Prostate cancer	3 (0.3)	1 (0.1)
Pulmonary embolism	3 (0.3)	1 (0.1)
Myocardial infarction	2 (0.2)	1 (0.1)
Confusional state	3 (0.3)	0

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Subject with two or more AEs with the same preferred term was counted only once for that preferred term. Cerebral microhaemorrhages include those deemed not ARIA-H by investigator. TEAEs were ordered by decreasing frequency in 10 mg/kg Biweekly group, then placebo group. MedDRA Version 25.0. AE = adverse event, TEAE = treatment-emergent adverse event, SAE = serious adverse event.

Table 44. Treatment-emergent serious adverse events by system organ class and preferred term (≥2 subjects in any treatment group with event by preferred term) - study 201 core - safety analysis set

MedDRA SOC Preferred Term	Placebo (N=245) n (%)	BAN2401 2.5 mg/kg Biweekly (N=52) n (%)	BAN2401 5 mg/kg Monthly (N=51) n (%)	BAN2401 5 mg/kg Biweekly (N=92) n (%)	BAN2401 10 mg/kg Monthly (N=253) n (%)	BAN2401 10 mg/kg Biweekly (N=161) n (%)	BAN2401 Total (N=609) n (%)
Subjects with any TESAE	43 (17.6)	10 (19.2)	4 (7.8)	16 (17.4)	31 (12.3)	25 (15.5)	86 (14.1)
General disorders and administration site conditions	2 (<1.0)	0	0	3 (3.3)	2 (<1.0)	4 (2.5)	9 (1.5)
Non-cardiac chest pain	0	0	0	0	2 (<1.0)	2 (1.2)	4 (<1.0)
Injury, poisoning and procedural complications	13 (5.3)	1 (1.9)	1 (2.0)	1 (1.1)	4 (1.6)	4 (2.5)	11 (1.8)
Fall	4 (1.6)	0	0	0	1 (<1.0)	0	1 (<1.0)
Subdural haematoma	2 (<1.0)	1 (1.9)	0	0	0	1 (<1.0)	2 (<1.0)
Musculoskeletal and connective tissue disorders	5 (2.0)	0	0	2 (2.2)	1 (<1.0)	3 (1.9)	6 (1.0)
Arthralgia	0	0	0	1 (1.1)	0	2 (1.2)	3 (<1.0)
Osteoarthritis	4 (1.6)	0	0	0	0	0	0
Nervous system disorders	9 (3.7)	1 (1.9)	2 (3.9)	6 (6.5)	6 (2.4)	6 (3.7)	21 (3.4)
Amyloid–related imaging abnormalities	0	0	0	0	1 (<1.0)	3 (1.9)	4 (<1.0)
Cerebral microhaemorrhage	0	0	0	0	0	2 (1.2)	2 (<1.0)
Syncope	3 (1.2)	0	0	1 (1.1)	1 (<1.0)	1 (<1.0)	3 (<1.0)
Transient ischaemic attack	1 (<1.0)	0	2 (3.9)	0	1 (<1.0)	1 (<1.0)	4 (<1.0)
Respiratory, thoracic and mediastinal disorders	1 (<1.0)	2 (3.8)	0	0	4 (1.6)	4 (2.5)	10 (1.6)
Dyspnoea	0	0	0	0	0	2 (1.2)	2 (<1.0)
Pulmonary embolism	0	0	0	0	1 (<1.0)	2 (1.2)	3 (<1.0)
Pulmonary mass	0	2 (3.8)	0	0	0	0	2 (<1.0)

A TEAE is defined as an AE that emerged during treatment or within 90 days following the last dose of study drug, having been absent at pretreatment (Baseline), or reemerged during treatment, having been present pretreatment but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subjects with 2 or more AEs in same SOC (or with same preferred term) were counted only once for that SOC (or preferred term). MedDRA Version 20.1. AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, TSEAE = treatment-emergent serious adverse event

In Study 201 Core there were no laboratory abnormalities considered serious TEAEs in the LEC10-BW group.

Results of **Pool Core** and **Pool LEC10BW** were overall consistent with studies 201 and 301 Core

Selected adverse events of interest to the proposed indication

Infusion-related reactions, skin rash, other hypersensitivity reactions, ARIA-E, and ARIA-H occurred at a lower frequency in PBO (156 [17.4%]) than LEC10-BW (379 [42.2%]) and most were considered treatment-related.

Table 45. List of preferred terms for adverse events of special interest - core study

AE of Special Interest	Preferred Term – MedDRA: 25.0
ARIA-E	Amyloid related imaging abnormality-edema/effusion
ARIA-H	
Macrohemorrhage	Cerebral haemorrhage Haemorrhage intracranial Thalamus haemorrhage
Superficial siderosis	Superficial siderosis of central nervous system
Cerebral microhemorrhage	Amyloid related imaging abnormality- microhemorrhage and hemosiderin deposit[a] Cerebellar microhaemorrhage
Infusion-related reactions	Infusion-related reaction
Skin rash	Rash[b]
Other hypersensitivity reactions	Hypersensitivity[b] Immediate post-injection reaction[b] Infusion-related hypersensitivity reaction[b] Infusion site hypersensitivity[b]
Suicidal behavior	Completed suicide Depression suicidal Intentional overdose Intentional self-injury Poisoning deliberate Suicidal behaviour Suicide attempt Suicide threat Assisted suicide Suspected suicide Suspected suicide attempt
Suicidal ideation	Self-injurious ideation Suicidal ideation

AE = adverse event, ARIA-E = amyloid related imaging abnormality-oedema/effusion, ARIA-H = amyloid related imaging abnormality- microhaemorrhage and hemosiderin deposit, MedDRA = medical dictionary for regulatory activities. a: This preferred term was not used for superficial siderosis. b: Relationship to study drug should be yes to the question 'Is there a reasonable possibility that the study drug caused the adverse event' in this study to be considered as AE of special interest

- **Infusion-Related Reactions**

Table 46. Summary of infusion-related reactions by maximum grade and use of preventative medications - study 301 core (safety analysis set)

NCI-CTCAE Grade	Placebo (N = 897) n (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n (%)
Any grade	66 (7.4)	237 (26.4)
Grade 1	41 (4.6)	78 (8.7)
Grade 2	25 (2.8)	149 (16.6)
Grade 3	0	6 (0.7)
Grade 4	0	1 (0.1)
Grade 5	0	0
Missing	0	3 (0.3)
Without Preventative Medication		
NCI-CTCAE Grade	**Placebo (N = 855) n (%)**	**Lecanemab 10 mg/kg Biweekly (N = 773) n (%)**
Any grade	57 (6.7)	137 (17.7)
Grade 1	40 (4.7)	72 (9.3)
Grade 2	17 (2.0)	57 (7.4)
Grade 3	0	5 (0.6)
Grade 4	0	1 (0.1)
Grade 5	0	0
Missing	0	2 (0.3)
With Preventative Medication		
NCI-CTCAE Grade	**Placebo (N = 42) n (%)**	**Lecanemab 10 mg/kg Biweekly (N = 125) n (%)**
Any grade	9 (21.4)	100 (80.0)
Grade 1	1 (2.4)	6 (4.8)
Grade 2	8 (19.0)	92 (73.6)
Grade 3	0	1 (0.8)
Grade 4	0	0
Grade 5	0	0
Missing	0	1 (0.8)

Grade 1: mild reaction, infusion interruption not indicated, intervention not indicated, Grade 2: infusion interruption or treatment indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], IV fluids); prophylactic medications indicated for <24 hours, Grade 3: prolonged (e.g., not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation required for clinical sequelae (e.g., renal impairment), Grade 4: life-threatening consequences; urgent treatment needed (e.g., vasopressor or ventilatory support), Grade 5: death. AEs are graded according to the CTCAE V4.0. "Without Preventative Medications" included subjects with no preventative medication at any visit. "With Preventative Medications" included subjects with preventative medication at least 1 visit. A subject with multiple severity grades within category was only counted under the maximum grade in each relevant category. Infusion-related reactions are defined if preferred term was infusion-related reaction or infusion site reaction.
AE = adverse event, NCI-CTCAE = Common Terminology Criteria for Adverse Events, IV = intravenous, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in treatment group, n = number of subjects at each visit, PBO =placebo.

There were few TEAEs of infusion-related reaction leading to study drug interruption (PBO 6/897 [0.7%], LEC10-BW 14/898 [1.6%]) or infusion interruption (PBO 1/897 [0.1%], LEC10-BW 9/898 [1.0%]); these subjects received subsequent infusions.

Most infusion reactions occurred at first infusion n=178 or at second infusion n= 56.

Infusion-related reactions were reported for 237 LEC10-BW subjects, 222 who continued to next visit.

There was a similar rate of recurrence regardless of use of preventative medications. Comparing subjects who took preventative medications with the first infusion-related reaction with those who did

not, there was no difference in preventing subsequent infusion-related reactions nor in severity of subsequent infusion-related reactions.

In **study 201**, the incidence of infusion-related reactions was lower in PBO (8/245 [3.3%]) than the lecanemab treatment groups, with a dose response seen with lecanemab (LEC2.5-BW 3/52 [5.8%], LEC5-M 4/51 [7.8%], LEC5-BW 12/92 [13.0%], LEC10-M 59/253 [23.3%], and LEC10-BW 32/161 [19.9%]. There was a trend of Grade 3 infusion-related reactions with higher doses of lecanemab (6 subjects total, LEC10-M 4/253 [1.6%] and LEC10-BW 2/161 [1.2%]). No subject experienced infusion-related reactions higher than Grade 3.

In **Pool Core**, consistently with Study 301 and 201, IRRs were mainly low grade (grade 1/2) with a dose-effect.

In **Pool LEC10 BW**, incidences were consistent with study 301: IRR occurred in 24.2% of patients and were mainly low grade (7.8% of patients had a grade 1 event, 15.5% of patients had a grade 2 events, 0.6% had a grade 3 event and 0.1% of patients (1 patient) had grade 4 event.

- **ARIA-E**

In **Study 301 Core**, the overall incidence of ARIA-E was lower in PBO (15 [1.7%]) than LEC10-BW (113/898 [12.6%]) (Table 47).

Table 47. Summary of treatment-emergent ARIA-E - study 301 core (safety analysis set)

ARIA Term	Placebo (N = 897) n/m (%)	Lecanemab 10 mg/kg Biweekly (N = 898) n/m (%)
ARIA-E	15 (1.7)	113 (12.6)
APOE4 noncarriers	1/286 (0.3)	15/278 (5.4)
APOE4 carriers	14/611 (2.3)	98/620 (15.8)
APOE4 heterozygous carriers	9/478 (1.9)	52/479 (10.9)
APOE4 homozygous carriers	5/133 (3.8)	46/141 (32.6)

A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.
A subject with 2 or more events is counted only once for that event.
APOE4 carrier and noncarrier status and genotype are based on actual lab data.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, N = number of subjects in treatment group, n = number of subjects with an event in each category, m = number of subjects in each category

ARIA-E events in PBO were randomly distributed over the course of treatment. For the first episode of ARIA-E, most cases of LEC10-BW treatment-emergent ARIA-E occurred within the first 3 months of treatment (LEC10-BW 80/113 [70.9%]) and was similar by APOE4 carrier status and genotype (Figure 26).

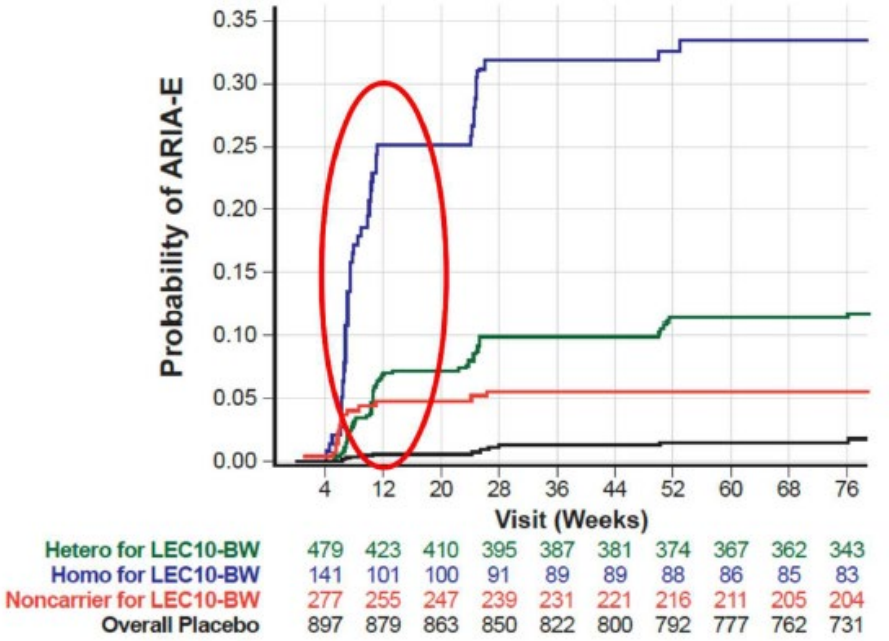


Figure 26. Kaplan-Meier curve of time to first ARIA-E event - study 301 core (safety analysis set)

ARIA = amyloid-related imaging abnormality-oedema/effusion, hetero = heterozygous, homo = homozygous

Most treatment-emergent ARIA-E were radiographically mild in severity (PBO 9/897 [1.0%]; LEC10-BW 37/898 [4.1%]) or moderate (PBO 6/897 [0.7%]; LEC10-BW 66/898 [7.3%]); with no subjects in PBO and 9 (1.0%) subjects in LEC10-BW categorized as having radiographically severe ARIA-E. The percentage of radiographically moderate severity ARIA-E was higher in the homozygous *APOE4* carriers.

Of those LEC10-BW subjects who reported ARIA-E, radiographic severity was as follows:

•Mild: 37/113 (32.7%)

•Moderate: 66/113 (58.4%)

•Severe: 9/113 (8.0%)

• *APOE4* noncarriers: moderate ARIA-E, 9/15 [60%] and no severe ARIA-E

•Heterozygous *APOE4* carriers: moderate ARIA-E, 24/52 (46.1%); severe ARIA-E, 2/52 (3.84%)

•Homozygous *APOE4* carriers: moderate ARIA-E, 33/46 (71.7%); severe ARIA-E, 7/46 (16.3%)

The incidence of symptomatic ARIA-E was low, with no subjects in PBO and 25/898 (2.8%) in LEC10-BW overall.

In both treatment groups, most subjects experienced ARIA-E without recurrence, with 1/897 (0.1%) PBO subject and 28/898 (3.1%) LEC10-BW subjects experiencing a second event. No PBO subjects and 4/898 (0.4%) LEC10-BW subjects experienced a third occurrence. One (1/898 [0.1%]) LEC10-BW subject (Subject 1604-1045) experienced 4 episodes of ARIA-E. The risk of recurrence increased with the number of *APOE4* alleles.

All 113 cases of ARIA-E in subjects treated with LEC10-BW resolved. In PBO, of the 15 subjects experiencing ARIA-E, 12 resolved and 3 remained ongoing.

Of the 69 LEC10-BW subjects who interrupted dosing, most resumed dosing during the study with a mean time to resolution of 3.0 months, except 7 subjects (7/898, 0.8% overall or 7/113, 61.9% LEC 10 BW with ARIA E).

Supportive **study 201** was less reliable regarding ARIA events considering the different discontinuations rules and the cessation of recruitment of APOE4 carriers. However, similar time to onset and severity were observed along with an influence of APOE4 status.

Overall in **Pool Core**, results were consistent with study 301. Incidence of ARIA-E increased with the dose and with the number of *APOE4* allele. The impact of *APOE4* status on severity is less clear, although it is noted *APOE4* non carriers did not experience severe ARIA-E.

The time to onset is within 3 months for the majority of events, and events resolved within 4 months in majority.

Overall, results of Pool **LEC10 BW** were consistent with results of study 301.

- **ARIA-H**

In study 301, the overall incidence of ARIA-H was lower in PBO (81/897 [9.0%]) than LEC10-BW (155/898 [17.3%]) (Table 48).

Table 48. Treatment-emergent ARIA-H subcategories - study 301 core (safety analysis set)

	Total		Isolated	
	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
ARIA-H (micro, macro, superficial)	81 (9.0)	155 (17.3)	70 (7.8)	80 (8.9)
Cerebral microhemorrhage	68 (7.6)	126 (14.0)	63 (7.0)	60 (6.7)
Superficial siderosis	21 (2.3)	50 (5.6)	13 (1.4)	23 (2.6)
Macrohemorrhage[a]	1 (0.1)	5 (0.6)	1 (0.1)	4 (0.4)
Symptomatic ARIA-H	2 (0.2)	13 (1.4)	2 (0.2)	4 (0.4)
ARIA-H by *APOE4* genotype				
APOE4 noncarrier, n/m (%)	12/286 (4.2)	33/278 (11.9)	11/286 (3.8)	23/278 (8.3)
APOE4 carrier, n/m (%)	69/611 (11.3)	122/620 (19.7)	59/611 (9.7)	57/620 (9.2)
APOE4 heterozygote, n/m (%)	41/478 (8.6)	67/479 (14.0)	35/478 (7.3)	40/479 (8.4)
APOE4 homozygote, n/m (%)	28/133 (21.1)	55/141 (39.0)	24/133 (18.0)	17/141 (12.1)

A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. A subject with two or more events is counted only once for that event. *APOE4* carrier and noncarrier status and genotype are based on actual lab data. The percentage by *APOE4* genotype is calculated as n/m*100 *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, N = number of subjects in treatment group, n = number of subjects with an event in each category, m = number of subjects in each category. TEAE = treatment-emergent adverse event. a: Incidence in this table is presented for TEAEs; considering not treatment emergent events, in Study 301 Core, the subtype of macrohaemorrhage (including not treatment emergent events) occurred in 2/897 subjects with PBO (0.2%) and 6/898 subjects with LEC10-BW (0.7%).

A breakdown of subtypes of treatment-emergent ARIA-H overall and by *APOE4* genotype is as follows:

- Macrohaemorrhage both on PBO and LEC10-BW occurred randomly throughout the course of treatment. One macrohaemorrhage occurred with LEC10-BW and concurrent anticoagulant medication (warfarin). Two subjects had macrohaemorrhage during follow up (≥30 days after last dose of study drug): one PBO subject had macrohaemorrhage 128 days after PBO discontinuation (last dose Day 239 – event Day 367). One LEC10-BW subject on anticoagulation had macrohaemorrhage 41 days after drug discontinuation (last dose Day 46 – event Day 86)
- Superficial siderosis: PBO 21/897 (2.3%); LEC10-BW 50/898 (5.6%), with exposure adjusted rates of PBO 0.02 and LEC10-BW 0.04.
    - PBO: 2/286 (0.7%) *APOE4* noncarriers, 13/478 (2.7%) heterozygous *APOE4* carriers, and 6/133 (4.5%) homozygous *APOE4* carriers
    - For LEC10-BW: 13/278 (4.7%) *APOE4* noncarriers, 19/479 (4.0%) heterozygous *APOE4* carriers, and 18/141 (12.8%) homozygous *APOE4* carriers
- Cerebral microhaemorrhage (preferred term of amyloid related imaging abnormality microhaemorrhages and hemosiderin deposits): PBO 69/897 (7.7%); LEC10-BW 126/898 (14%), with exposure adjusted rates of PBO 0.06 and LEC10-BW 0.11.
    - PBO: 9/286 (3.1%) *APOE4* noncarriers, 34/478 (7.1%) were heterozygous *APOE4* carriers, and 25/133 (18.8%) were homozygous *APOE4* carriers
    - LEC10-BW: 20/278 (7.2%) *APOE4* noncarriers, 58/479 (12.1%) heterozygous *APOE4* carriers, and 48/141 (34.0%) homozygous *APOE4* carriers
- Cerebral microhaemorrhage (preferred term of cerebellar microhaemorrhage): no events in either treatment group
- Cerebral microhaemorrhage >10: PBO 1/897 (0.1%); LEC10-BW 27/898 (3.0%)
    - PBO: 0/286 (0%) *APOE4* noncarriers, 1/478 (0.2%) *APOE4* carriers, and 0/133 (0%) homozygous *APOE4* carriers
    - LEC10-BW: 0/278 (0%) *APOE4* noncarriers, 8/479 (1.7%) heterozygous *APOE4* carriers, and 19/141 (13.5%) homozygous *APOE4* carriers
- Cerebral microhaemorrhage ≤10: PBO 68/897 (7.6%); LEC10-BW 119/898 (13.3%)
    - PBO: 9/286 (3.1%) *APOE4* noncarriers, 34/478 (7.1%) *APOE4* carriers, and 25/133 (18.8%) homozygous *APOE4* carriers
    - LEC10-BW: 20/278 (7.2%) subjects were *APOE4* noncarriers, 57/479 (11.9%) were heterozygous *APOE4* carriers, and 42/141 (29.8%) were homozygous *APOE4* carriers

Most cases of ARIA-H with PBO or LEC10-BW were ongoing at the end of the Core Study. All cases of macrohaemorrhage with PBO or LEC10-BW were ongoing.

Most treatment-emergent ARIA-H were radiographically mild (PBO 73/897 [8.1%]; LEC10-BW 97/898 [10.8%]) to moderate (PBO 5/897 [0.6%]; LEC10-BW 26/898 [2.9%]) in severity; with 3 (0.3%) subjects on PBO and 32 (3.6%) on LEC10-BW reporting severe ARIA-H, mostly driven by any microhaemorrhage event that resulted in a cumulative number greater than 10 microhaemorrhages (27/898 [3.0%]). Similar trends were observed in all ARIA-H subcategories.

Of those LEC10-BW subjects who reported ARIA-H, radiographic severity was as follows:

- Mild: 97/155 [62.6%])
- Moderate: 26/155 [16.8%])
- Severe: 32/155 (20.6%) on LEC10-BW reporting severe ARIA-H, mostly driven by any microhaemorrhage event that resulted in a cumulative number greater than 10 microhaemorrhages (27/155 [17.4%]).

In both treatment groups, most ARIA-H was asymptomatic overall and across the subtypes. The asymptomatic rates among the subjects with ARIA-H were:

- Asymptomatic macrohaemorrhage: PBO 1/1 (100%; this event was fatal, although no prior symptoms were reported), LEC10-BW 3/5 (60%)
- Asymptomatic superficial siderosis: PBO 21/21 (100%), LEC10-BW 48/50 (96.0%)
- Asymptomatic cerebral microhaemorrhage: PBO 66/68 (97.1%), LEC10-BW 117/126 (92.8%).

Symptomatic ARIA-H was reported in 2/897 (0.2%) subjects in PBO and 13/898 (1.4%) subjects in LEC10-BW. Among subjects with ARIA-H, 13/155 (8.4%) were symptomatic in LEC10-BW and 2/82 (2.4%) in placebo. Preferred terms for symptoms occurring in more than 1 subject in LEC10-BW were headache (4 subjects), dizziness (3 subjects), and confusional state (2 subjects).

Table 49. ARIA-H macrohaemorrhages - study 301 core (safety analysis set)

Subject Identifier	Treatment Group	TE	Anti coag	Antiplatelet	ASA	Isolated ARIA-H or Concurrent with ARIA-E	*APOE4* Carrier Status (genotype)	Onset Day	Outcome	Symptomatic (Y/N)
[redacted]	LEC10-BW	Y	N	Y	N	Concurrent	+/+	48	Not recovered/not resolved	N
[redacted]	PBO	N (stopped for ARIA 61 days before)	N	N	N	Concurrent	+/-	300	Recovering/Resolving	Y
[redacted]	LEC10-BW	Y	N	N	N	Isolated	+/-	441	Not resolved	Y
[redacted]	PBO	Y	N	N	Y	Isolated	-/-	unknown	Fatal	N
[redacted]	LEC10-BW	N (stopped for ARIA 39 days before)	Y	N	N	Concurrent	+/-	85	Recovering/Resolving	Y
[redacted]	LEC10-BW	Y	N	N	N	Isolated	-/-	439	Not resolved	Y
[redacted]	LEC10-BW	Y	Y	N	Y	Isolated	+/+	175	Recovering/Resolving	N
[redacted]	LEC10-BW	Y	N	N	N	Isolated	+/-	173	Recovering/Resolving	N

Concurrent is defined as overlapping in the AE duration of 2 ARIA events. Antiplatelet use excludes aspirin. Aspirin use is designated in ASA column. *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, ASA = aspirin, LEC10-BW = 10 mg/kg biweekly, PBO = placebo, TEAE = treatment-emergent adverse event

The overall incidence of serious TEAEs due to ARIA-H were 1/897 (0.1%) in PBO and 5/898 (0.6%) in LEC10-BW. Thus, in patients who experienced an ARIA-H, serious events were reported in 1/81 patients (1.2%) in PBO and in 5/155 (3.2%) in LEC10-BW. The incidence of serious ARIA-H was lower in the heterozygous *APOE4* carriers (PBO 0/478; LEC10-BW 1/479 [0.2%] and *APOE4* noncarriers (PBO 1/286 [0.3%]; LEC10-BW 2/278 [0.7%]) than in homozygous *APOE4* carriers (PBO 0/133 [0%]; LEC10-BW 2/141 [1.4%]).

Table 50. Serious adverse events of ARIA-H - study 301 core (safety analysis set)

Subject Identifier	Treatment Group	Preferred Term or Subcategory	Isolated ARIA-H or Concurrent with ARIA-E	*APOE4* Carrier Status (Genotype)
[redacted]	LEC10-BW	Cerebral haemorrhage	Concurrent	Carrier (homozygous)
[redacted]	LEC10-BW	Amyloid related imaging abnormality-microhemorrhages and haemosiderin deposits	Concurrent	Noncarrier
[redacted]	LEC10-BW	Cerebral hemorrhage	Isolated	Carrier (heterozygous)
[redacted]	LEC10-BW	Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	Concurrent	Carrier (homozygous)
[redacted]	LEC10-BW	Cerebral hemorrhage	Isolated	Noncarrier
[redacted]	PBO	Hemorrhage intracranial	Isolated	Noncarrier

Concurrent is defined as overlapping in the AE duration of 2 ARIA events.

APOE4 = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality oedema/ effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, LEC10-BW = 10 mg/kg biweekly, N = number of subjects in treatment group, n = number of subjects for each category, PBO = placebo, TEAE = treatment-emergent adverse event.

In **study 201**, incidence of ARIA-H was similar in placebo arm (4.9%) and in LEC10 BW arm (6.2%). However, incidence in other lecanemab arm were higher (13.7% in LEC5 M, 14.1% in LEC5 BW and 9.5% in LEC10 M). Of importance in study 201, homozygous APOE4 carriers were required to be discontinued by Health authorities. In addition, as per study 201 protocol, patients were to be discontinued upon the first occurrence of ARIA-H. Therefore, it is considered that the reduced number of homozygous APOE4 carriers, along with the fact that discontinuation rules were different from study 301, a comparison is difficult. The incidence of ARIA-H may have been impacted by the reduce number of patients homozygous APOE4 carriers.

Overall, **Pool Core** is consistent with the results of study 301. Total ARIA-H occurred in 165/1059 (15.6%) in the lecanemab group and 93/1142 (8.1%) in the placebo group. Isolated ARIA-H occurred at a similar incidence in placebo (7.1%) and LEC10 BW (7.9%) groups whereas incidence of concurrent ARIA-E and ARIA-H were higher in LEC10 BW group (7.6%) than in placebo group (0.9%) leading to overall twice higher incidence of ARIA-H in LEC10 BW group (15.6%) than in placebo group (8.1%).

For each subcategory of ARIA-H (macrohaemorrhage, superficial siderosis and cerebral microhaemorrhage) events were more frequent in LEC10 BW group than in placebo. Noting that incidences in LEC10 BW may be under-evaluated considering the reduced rate of homozygous APOE4 carrier in study 201.

In the pool Core, serious events of ARIA-H were observed in 7/165 patients with ARIA-H treated with lecanemab and in 1/93 on placebo.

Incidence of symptomatic ARIA-H was 13/165 (7.9%) for lecanemab and 2/93 (2.1%) for placebo) . among patients who experienced an ARIA-H event.

Finally, **Pool LEC10 BW** was consistent with result of study 301. Incidence of ARIA-H increased with the number of APOE4 alleles.

ARIA-E, ARIA-H (macrohaemorrhage and hemosiderosis), and macrohaemorrhage and antithrombotic use.

Table 51. ARIA incidence by use of antiplatelet or anticoagulant therapy - study 301 core (safety analysis set)

	ARIA		ARIA-E		Micro		SS		Macro	
	PBO	LEC10-BW	PBO	LEC10-BW	PBO	LEC10-BW	PBO	LEC10-BW	PBO	LEC10-BW
Not on antiplatelet or anticoagulation at any time	52/586 (8.9%)	123/564 (21.8%)	9/586 (1.5%)	74/564 (13.1%)	42/586 (7.2%)	79/564 (14%)	13/586 (2.2%)	32/564 (5.7%)	0/586	3/564 (0.5%)
Event post any antiplatelet (aspirin or non-aspirin)	23/237 (9.7%)	45/251 (17.9%)	2/237 (0.84%)	26/251 (10.4%)	18/237 (7.6%)	31/251 (12.4%)	5/237 (2.1%)	13/251 (5.2%)	1/237 (0.4%)	1/251 (0.4%)
Event post any anticoagulation (alone or with antiplatelet)	8/74 (10.8%)	11/83 (13.3%)	2/74 (2.7%)	4/83 (4.8%)	7/74 (9.5%)	8/83 (9.6%)	2/74 (2.7%)	3/83 (3.6%)	0/74	1/83 (1.2%)

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, micro = microhaemorrhage, macro = macrohaemorrhage, PBO = placebo, SS = superficial siderosis.

2.6.8.4. Laboratory findings

Chemistry

In **Study 301 Core**, Baseline chemistry values were within normal ranges. There were no clinically meaningful changes over time for mean values for PBO or LEC10-BW. There were no notable shifts from Baseline with respect to normal, low, and high values. The incidence of treatment-emergent markedly abnormal chemistry values was low and similar between PBO and LEC10-BW, except for markedly Abnormal Low calcium, which occurred more often in the lecanemab arm (1.8%) than in the PBO arm (0.9%).

There was 1 case of Hy's Law in Study 301 Core (PBO 1/897 [0.11%]) with aetiology of herbal medicines, and 0/898 in LEC10-BW).

In **study 201 Core**, baseline chemistry values were within normal ranges and that no clinically meaningful changes over time were observed, except that more patients receiving lecanemab had markedly abnormal low calcium than patients receiving PBO (though without increased incidence with increasing dose)

Haematology

In **Study 301 Core**, Baseline haematology values were within normal ranges. There were no clinically meaningful changes over time for mean values in PBO and LEC10-BW.

There were no notable shifts from Baseline with respect to normal, low and high values.

The incidence of treatment-emergent markedly abnormal haematology values was low and similar between PBO and LEC10-BW. A summary of subjects with 1 or more haematology laboratory value exceeding specified high or low values (level 1 to level 3) is presented.

In **Study 201 Core**, Baseline haematology values were within normal ranges for all haematology parameters. There were no clinically meaningful changes over time for mean values in the treatment groups. There were no dose-related trends and no changes that were considered clinically meaningful. Neutrophils were increased and lymphocytes were transiently decreased after the first dose compared to Baseline in subjects who received lecanemab. These are likely due to infusion-related reaction and

the changes were not considered clinically significant as they only occurred after the first dose and did not occur during the remainder of the treatment period.

Urinalysis

In **Study 301 Core**, Baseline urinalysis values were within normal ranges. There were no clinically meaningful changes over time for mean values for PBO and LEC10-BW. There were no notable shifts from Baseline with respect to normal, low, and high values. There were no treatment-emergent markedly abnormal urinalysis values.

In study 201, it is acknowledged that baseline urinalysis values were within normal ranges and that there were no clinically meaningful changes over time for mean values in the treatment groups.

2.6.8.5. Vital signs, physical findings and other observations related to safety

- Vital signs

In **study 301 and 201 Core**, mean baseline values of vital signs were within normal ranges and no clinically meaningful changes over time were observed in placebo and LEC10-BW. A slight trend of higher incidence of clinically notable high temperature was observed in LEC10 BW arm (0.7%) compared to placebo arm (0%). These events were observed only post dose, it is acknowledged that it can be considered to be part of infusion-related reactions.

- ECG

In **study 301 and 201 Core**, ECG values were within normal ranges and no clinically meaningful changes over time were observed in placebo and LEC10-BW arms.

- Suicidality

Overall in subjects with EAD in study **301 and 201 core**, suicidal ideation of various grades (C-SSRS) was similar between lecanemab and placebo arms although there was one event of suicidal attempt in LEC10 BW arm in study 301.

2.6.8.6. In vitro biomarker test for patient selection for safety

This part was not discussed by the applicant. Currently, only a suggestion to assess APOE4 status is described in the SmPC whereas a mandatory requirement was requested and supported by the SAG-N.

2.6.8.7. Safety in special populations

The Applicant provided an analysis of special population by age, race, APOE carriers (non-carriers, heterozygous, homozygous) and clinical subcategories (MCI and mild AD), region, and use of AD symptomatic medication. The most relevant information regards the APOE status, see tables below.

Table 52. Analysis of the incidence, timing and recurrence of symptomatic and asymptomatic ARIA-E events by genotype – study 301 core

	PBO				LEC10-BW			
ARIA-E	Overall (N=897) n (%)	Non-carrier (N=286) n (%)	Hetero (N=478) n (%)	Homo (N=133) n (%)	Overall (N=898) n (%)	Non-carrier (N=278) n (%)	Hetero (N=479) n (%)	Homo (N=141) n (%)
Incidence	15 (1.7)	1 (0.3)	9 (1.9)	5 (3.8)	113 (12.6)	15 (5.4)	52 (10.9)	46 (32.6)
Symptomatic	0 (0)	0 (0)	0 (0)	0 (0)	25 (2.8)	4 (1.4)	8 (1.7)	13 (9.2)
Asymptomatic	15 (1.7)	1 (0.3)	9 (1.9)	5 (3.8)	88 (9.8)	11 (4.0)	44 (9.2)	33 (23.4)
Timing (≤27 week visits)a	10/15 (66.7)	1/1 (100)	5/9 (55.6)	4/5 (80.0)	104/113 (92.0)	15/15 (100)	45/52 (86.5)	44/46 (95.7)
Symptomatic[a]	0/0 (0)	0/0 (0)	0/0 (0)	0/0 (0)	17/17 (100)	3/3 (100)	6/6 (100)	8/8 (100)
Asymptomatic[a]	10/15 (66.7)	1/1 (100)	5/9 (55.6)	4/5 (80.0)	87/96 (90.6)	12/12 (100)	39/46 (84.8)	36/38 (94.7)
Recurrent event	1 (0.1)	0 (0)	0 (0)	1 (0.8)	28 (3.1)	1 (0.4)	7 (1.5)	20 (14.2)
Symptomatic (multiple events)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)	2 (1.4)
Symptomatic (at least one event)	0 (0)	0 (0)	0 (0)	0 (0)	10 (1.1)	1 (0.4)	2 (0.4)	7 (5.0)
Asymptomatic (all events)	1 (0.1)	0 (0)	0 (0)	1 (0.8)	18 (2.0)	0 (0)	5 (1.0)	13 (9.2)

ARIA-E = amyloid-related imaging abnormalities – oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.
a: Percentage is based on subjects with relevant ARIA-E. Symptomatic/asymptomatic is classified based on first ARIA-E at onset.

Table 53. Analysis of the incidence, timing and recurrence of symptomatic and asymptomatic ARIA-H events by genotype – study 301 core

	PBO				LEC10-BW			
ARIA-H	Overall (N=897) n (%)	Non-carrier (N=286) n (%)	Hetero (N=478) n (%)	Homo (N=133) n (%)	Overall (N=898) n (%)	Non-carrier (N=278) n (%)	Hetero (N=479) n (%)	Homo (N=141) n (%)
Incidence	81 (9.0)	12 (4.2)	41 (8.6)	28 (21.1)	155 (17.3)	33 (11.9)	67 (14.0)	55 (39.0)
Symptomatic	2 (0.2)	0 (0)	1 (0.2)	1 (0.8)	13 (1.4)	3 (1.1)	5 (1.0)	5 (3.5)
Asymptomatic	79 (8.8)	12 (4.2)	40 (8.4)	27 (20.3)	142 (15.8)	30 (10.8)	62 (12.9)	50 (35.5)
Timing (≤27 wk visits)[a]	45/81 (55.6)	6/12 (50.0)	22/41 (53.7)	17/28 (60.7)	110/155 (71.0)	20/33 (60.6)	44/67 (65.7)	46/55 (83.6)
Symptomatic[a]	0/1 (0)	0/0 (0)	0/0 (0)	0/1 (0)	6/9 (66.7)	2/3 (66.7)	1/3 (33.3)	3/3 (100)
Asymptomatic[a]	45/80 (56.3)	6/12 (50.0)	22/41 (53.7)	17/27 (63.0)	104/146 (71.2)	18/30 (60.0)	43/64 (67.2)	43/52 (82.7)
Timing (≤65 wk visits)[a]	67/81 (82.7)	9/12 (75.0)	33/41 (80.5)	25/28 (89.3)	138/155 (89.0)	25/33 (75.8)	60/67 (89.6)	53/55 (96.4)
Symptomatic[a]	1/1 (100)	0/0 (0)	0/0 (0)	1/1 (100)	9/9 (100)	3/3 (100)	3/3 (100)	3/3 (100)
Asymptomatic[a]	66/80 (82.5)	9/12 (75.0)	33/41 (80.5)	24/27 (88.9)	129/146 (88.4)	22/30 (73.3)	57/64 (89.1)	50/52 (96.2)
Timing (>65 wk visits)[a]	14/81 (17.3)	3/12 (25.0)	8/41 (19.5)	3/28 (10.7)	17/155 (11.0)	8/33 (24.2)	7/67 (10.4)	2/55 (3.6)

Symptomatic[a]	0/1 (0)	0/0 (0)	0/0 (0)	0/1 (0)	0/9 (0)	0/3 (0)	0/3 (0)	0/3 (0)
Asymptomatic[a]	14/80 (17.5)	3/12 (25.0)	8/41 (19.5)	3/27 (11.1)	17/146 (11.6)	8/30 (26.7)	7/64 (10.9)	2/52 (3.8)
Recurrent event	24 (2.7)	1 (0.3)	11 (2.3)	12 (9.0)	61 (6.8)	6 (2.2)	25 (5.2)	31 (22.0)
Symptomatic (multiple events)	1 (0.1)	0 (0)	0 (0)	1 (0.8)	1 (0.1)	0 (0)	0 (0)	1 (0.7)
Symptomatic (at least one event)	2 (0.2)	0 (0)	1 (0.2)	1 (0.8)	7 (0.8)	0 (0)	3 (0.6)	4 (2.8)
Asymptomatic (all events)	22 (2.5)	1 (0.3)	10 (2.1)	11 (8.3)	55 (6.1)	6 (2.2)	22 (4.6)	27 (19.2)

ARIA-H = amyloid-related imaging abnormalities – haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.
a: Percentage is based on subjects with relevant ARIA-H. Symptomatic/asymptomatic is classified based on first ARIA-H at onset.

2.6.8.8. Immunological events

Study 301 Core

Baseline ADA and Nab: the ADA prevalence rate was 5.0%, indicating a background pre-existence of immune response in the study population. The maximum ADA titre at baseline was ≥2000 in LEC10-BW. A small and similar proportion of the subjects in PBO (3/46 [6.5%]) and LEC10-BW (2/44 [4.5%]) who had baseline ADA were positive for Nab. The NAb prevalence rate was 0.3% with maximum titre of 270 reported for a single subject.

Postbaseline ADA and Nab:

- ADA

Incidence: Postbaseline 5.5% (49/884) subjects were treatment-emergent ADA positive, 48.5% (429/884) subjects were ADA negative conclusive, and 45.9% (406/884) subjects were ADA negative inconclusive.

Titre: ADA titres were low (Q1, Q3 of maximum ADA titres were 16 and 400, with 3 subjects having titre ≥2000) and tended to decrease with longer duration of dosing.

Induced/Boosted: Treatment-boosted ADA rates for LEC10-BW were low. Of the 49 treatment-emergent ADA-positive subjects, 43 (87.8%) were treatment-induced, 6 (12.2%) were treatment-boosted, and none were positive (i.e., where the ADA response cannot be determined as treatment-induced or treatment-boosted).

Persistence: The majority of the treatment-induced ADA were considered to be transient ADA positive (29/43, 67.4%) and the remainder were persistent ADA positive (14/43 [re

%])

Onset: Of the 43 LEC10-BW subjects with treatment-induced ADA, most developed in the early, within the first 13 weeks of treatment (30.2%) or middle part of treatment, between week 13 and week 53 (51.2%).

- NAb

Incidence: Of the subjects with ADA, few had NAb. Postbaseline 2/49 (4.1%) subjects were treatment-emergent NAb positive, 47/49 (95.9%) subjects were NAb negative conclusive, and none were NAb negative inconclusive.

Titre: NAb-titres were low (Q1, Q3 of maximum NAb titres were 10, and 10, with 1 subject having a titre <10, and 1 subject with titre 10.

Induced/Boosted: There were no treatment boosted NAb for LEC10-BW. Both of the treatment-emergent NAb-positive subjects had treatment-induced NAb.

Persistence: One of the 2 treatment-induced NAb subjects was considered to be transient NAb positive and with the other subject as persistent NAb positive.

Onset: One subject developed NAb in the middle of treatment and the other subject developed NAb after 53 weeks of treatment.

In **Study 201 Core**, the incidence of treatment-emergent positive ADA in LEC10-BW was 40.9% with low titres (Q1, Q3 of maximum ADA titres were 5, and 125). 25.4% were treatment-emergent NAb positive, with low titres (≤5).

2.6.8.9. Safety related to drug-drug interactions and other interactions

Lecanemab is a mAb that targets aggregated soluble and insoluble forms of Aβ and is not expected to be involved in cytokine modulated pathways. Elimination of lecanemab occur through normal degradation pathways for immunoglobulins and the clearance should not be affected by small molecule concomitant medications. Therefore, it is not expected that lecanemab will cause, or be susceptible to, drug interactions with concomitantly administered agents. For these reasons, no specific clinical or nonclinical drug-drug interaction studies have been conducted for lecanemab and none are planned.

2.6.8.10. Discontinuation due to adverse events

- Discontinuation

In study 301 Core, the incidence of TEAE leading to treatment discontinuation was similar in both treatment arms (3.1% in LEC10 BW arm and 2.9% in placebo arm 2.9%).

Table 54. Treatment-emergent adverse events leading to discontinuation of study drug by system organ class and preferred term occurring in ≥2 subjects in any treatment group - study 301 core (safety analysis set)

MedDRA System Organ Class Preferred Term	Placebo (N=897) n (%)	Lecanemab 10 mg/kg Biweekly (N=898) n (%)
Subjects with any TEAE leading to discontinuation from study drug	26 (2.9)	62 (6.9)
Cardiac disorders		
Myocardial infarction	2 (0.2)	1 (0.1)
Injury, poisoning and procedural complications		
Infusion-related reaction	1 (0.1)	12 (1.3)
Subdural hematoma	2 (0.2)	1 (0.1)
Nervous system disorders		
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	1 (0.1)	15 (1.7)
Amyloid related imaging abnormality-oedema/effusion	0	13 (1.4)
Superficial siderosis of central nervous system	0	4 (0.4)
Psychiatric disorders		
Depression	0	2 (0.2)

A TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. Subject with two or more AEs in the same system organ class (or with the same preferred term) was counted only once for that system organ class (or preferred term). Cerebral microhaemorrhages include those deemed not ARIA-H by investigator. MedDRA Version 25.0. AE = adverse event, ARIA–H = amyloid-related imaging abnormality-haemorrhage, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in treatment group, n = number of subjects at each visit, TEAE = treatment-emergent adverse event.

In study 201 Core, the incidence of TEAE leading to drug discontinuation was higher in all lecanemab arms than in placebo arm. Furthermore, in all arms (placebo and lecanemab groups), the incidence of TEAE leading to discontinuation was higher than in study 301 Core. This is likely due to protocol-required discontinuations due to ARIA–E.

In Pool Core, results were overall consistent with study 301 Core with however a higher incidence of TEAEs probably due to results of study Core 201 for which protocol requirement were more stringent with regards to discontinuation due to ARIA.

- Dose Interruption or infusion interruption

In study 301 Core, the incidence of TEAEs leading to study drug interruption was higher in LEC10-BW arm (19.5%) than in placebo arm (7.9%). This difference was mostly due to events of ARIA-E, ARIA-H (microhaemorrhage).

In study Core 201, incidence of TEAEs leading to study drug dose interruption was balanced across arms. This discrepancy with study 301 is likely due to the fact that patients were required to discontinue treatment in case of ARIA in study 201 but were able to continue dosing as per study 301 protocol if the events were mild.

2.6.8.11. Post marketing experience

At the time of the submission, lecanemab was not currently marketed in any territory, the applicant presented limited postmarketing data during the evaluation procedure.

2.6.9. Discussion on clinical safety

Safety data for this submission comes mainly from a pivotal randomized phase 3 study (study 301 Core) and a supportive phase 2 study (study 201 Core) in patients with Early Alzheimer Disease (MCI due to AD and mild AD dementia) which is the intended population. The studies (including their extensions) are described above.

In addition, pooled data from the phase 2 and the pivotal phase 3 study were presented, allowing to analyse expanded safety data in the relevant population. The Pool Core includes all patients from Core parts of both studies (n=1142 in placebo group and n=1059 in LEC10-BW group). The Pool LEC10 BW includes all patients who received lecanemab at the intended dose of 10mg/kg (n=1694) in the Core or OLE parts of studies 301 and 201.

Exposure

In study 301, the mean (SD) duration of exposure was similar in both treatment arms, with 16.49 (3.93) months and 15.74 (5.04) months in placebo and lecanemab arm respectively. Median duration of exposure was also similar between both treatments group (18.03 months). Overall, in study 301, the extent of exposure including long term exposure was comparable between both treatments arms.

In total, in Pool LEC10 BW, 1578, 1014 and 828 subjects were exposed to lecanemab at the intended dose for ≥ 6, ≥ 12 and ≥ 18 months respectively which is considered compliant with ICHE1.

To be noted, patients who received a lower dose than 10mg/kg BW in the Core 201, and transitioned to 10mg/kg later on, were accounted for as exposed in the full period (Core+OLE), excluding the gap time in between. Therefore, the overviewed total exposure is a bit overestimated in the Pool LEC10 BW.

Overall, in study 301, demography and baseline characteristics were similar between both treatment arms. Indeed, in placebo and LEC10 BW respectively, mean (SD) age was 71.1 (7.79) years and 71.4 (7.88) years, and female represented 53.1 % and 51.4 % of the population. The majority of patients were white (77.6% and 76.3% respectively in placebo and LEC10 BW patients) or Asian (16.7% and 17% respectively in placebo and LEC10 BW patients). MCI due to AD and Mild AD were both represented in the safety population and balanced between treatment groups. The majority of patients were *APOE4* carriers (68.1% and 69.0% in placebo and LEC10 BW respectively) of which most patients were heterozygous (53.3% in both groups). Thus, *APOE4* status were balanced between both treatment groups.

The use of AD symptomatic medication was also balanced between both treatment groups with 53.2% and 51.9% in placebo and LEC10 BW respectively using symptomatic medication at baseline.

In supportive study 201, *APOE4* carriers represented only 30% of LEC10 BW group when they represented 71% of patients in placebo group, due to the changes in allocation discussed above. Considering that *APOE4* is a risk factor for ARIA, results from study 201 should be carefully considered with regards to such adverse events, as ARIA could be potentially underrated. Results from Pool Core should be also carefully considered as patients from study 201 represents 15% of the LEC10 BW group.

In study 301, the frequency of concomitant anti-thrombotic treatment was similar between placebo and LEC10-BW. However, some differences appeared in the use of paracetamol (24.3% in placebo group and 31.8% in LEC10 BW) and in the use of diphenhydramin (3% in placebo group vs 8.8% in LEC10 BW), which can be attributed to the management of IRRs.

Adverse events

Treatment emergent adverse event

In study 301, the incidence of Treatment Emergent Adverse Events (TEAE) was higher in LEC10 BW arm (88.9%) than in placebo arm (81.9%). Although the incidence of severe TEAEs was similar between both treatment arms (7.5% in LEC10 BW and 6.8% in placebo), the incidence of serious TEAEs was higher in LEC10 BW (14%) compared to placebo arm (11.3%), mainly SAEs requiring inpatient hospitalisation or prolongation of existing hospitalisation.

Overall, the more frequent TEAEs occurring in LEC10 BW arm were IRR (26.3%), ARIA-H-microhaemorrhage and hemosiderin deposit (14.0%), ARIA-E (12.6%), headache (11.1%) and fall (10.4%).

A difference compared to placebo was observed for IRR (7.1%), ARIA-H (7.7%), ARIA-E (1.7%) and headache (8.1%). Other common TEAEs included urinary tract infection, COVID-19, back pain, arthralgia, superficial siderosis of central nervous system, dizziness, diarrhoea and anxiety. All but superficial siderosis of central nervous system were observed at a similar incidence in both treatment arm. Indeed, "superficial siderosis of central nervous system" was observed in 5.6% of patients in LEC10 BW arm and in 2.5% of patient in placebo arm.

Anxiety (4.2 vs 5.0%), fatigue (2.7 vs 4.1%), nausea (2.8 vs 3.5%), vomiting (2.5 vs 3.2%), rash (1.9 vs 3.2%), insomnia (2.3 vs 2.7%), atrial fibrillation (1.6 vs 2.7%), haematuria (0.8 vs 2.3%) and syncope (1.3 vs 2.0%) occurred more often in the lecanemab 10 BW arm than in the placebo group.

In the TEAEs list of SOC terms more cardiac events occurred in the LEC10 BW arm than in the placebo (6.8% vs 9.5%). Parts of this is explained by atrial fibrillation 1.6% vs 2.7% which is stated in the SmPC. The remaining differences are driven by atrioventricular block first degree (0.4 vs 0.9%), bundle branch block left (0.3 vs 0.9%), sinus bradycardia (0.3 vs 0.8%) and angina pectoris (0,3% vs 1%) all occurred more often in the LEC10 BW. In addition, also prolonged QT occurred in 6 (0.7%) in the LEC10 BW vs 0 in the placebo arm. Noted is also that syncope occurs more often in LEC10-BW (2%) vs PBO (1.3%). Based on the low rates of cardiovascular events, the applicant proposed no risk minimisation, which is not endorsed. However, since the incidences of cardiac events points in opposite directions between the studies it can be accepted that angina pectoris, syncope, and QT prolongation in the LEC10 BW arm in study 301 may be due to chance alone, are not considered ADRs. Nevertheless, a certain level of uncertainty remains since observations in the pivotal study 301 might be more accurate than observations in study 201 due to a much higher number of patients. The applicant agreed to further monitor events of angina pectoris, syncope, and QT prolongation in Periodic Safety Update Reports (PSURs) in case of a favourable outcome of the MA by the CHMP.

The incidence of treatment-related TEAEs was twice higher in LEC10 BW arm (44.7%) than in placebo arm (22.0%), and the most commonly reported (≥2%) treatment-related TEAEs were IRR, ARIA-H, ARIA-E and superficial siderosis of central nervous system. In addition, 4 events of cerebral haemorrhage in LEC10 BW arm and none in placebo were considered related to study treatment. The applicant confirmed that these events were part of ARIA-H.

In supportive study 201 Core, the most frequent TEAEs were similar to study 301, with a dose effect for incidence of IRR (placebo 3.3%, LEC2.5 BW 5.8%, LEC5 M 7.8%, LEC5 BW 12%, LEC10 M 23.3% and LEC10 BW 23.3%). To be noted, incidence of ARIA-E and especially ARIA-H (4.5% in placebo and

5.6% in LEC10 BW) was markedly lower than in study 301. This is probably due to the fact that 1) discontinuation requirement were stricter as per protocol, and 2) the reduced number of *APOE4* carriers, which is a risk factor for ARIAs. In addition, a dose-effect was observed with increasing incidence of TEAEs of special interest with increasing doses (13.5% in LEC2.5 BW, 19.6% in LEC5 M, 28.3% in LEC5 BW and 34.8% in LEC10 M).

Treatment-Emergent Adverse Events (TEAE) were defined as AEs starting on or after the first dose of study drug through the last visit or AEs that worsen in severity during treatment. In study 301 (Core + OLE) and Study 201 (OLE) AEs were included if they occurred during treatment or within 30 days following the last dose of study drug. Whereas in study 201 Core it was AEs that happened during treatment or within 90 days following the last dose of study drug. However, since no obvious concerning AE occurred in the period from day 30 to 90 in study 201, the shorter period for which an AE was registered as treatment emergent in study 301 seems acceptable.

Results of Pool Core were overall consistent with study 301. In Pool LEC10 BW, atrial fibrillation was observed at a slightly higher, although almost double, incidence in LEC10 BW group (2.8%) than in placebo group (1.5%). No event of atrial fibrillation was considered treatment related in LEC10 BW arm from study 301 (one event considered related in placebo arm). However, in study 201, 2 events of atrial fibrillation were considered related to lecanemab: one in LEC10 BW arm (mild) and one in LEC10 M (moderate). Based on the consistency of higher incidence of atrial fibrillation in LEC10-BW compared to placebo arm through studies, the applicant included atrial fibrillation in section 4.8 of the proposed SmPC as an adverse drug reaction.

More generally, the process for assessing which TEAEs were related to study drug were subject to change: First TEAEs that occurred in at least 2% of LEC10-BW subjects and at a rate higher than or equal to 2% more than in the PBO group were selected, but then it was decided that TEAEs that occurred in at least 5% of subjects LEC10-BW and at ≥ 2% higher than PBO would be more appropriate. Based on this the applicant has provided a list of TEAE with incidence ≥5% and ≥2% higher than placebo group, but the precise link to the assessment of causality is not clear. In the proposed SmPC section 4.8 the frequencies mentioned are identical to the TEAEs e.g. 26.3% IRR, 14% ARIA-H (microhaemorrhage and hemosiderin deposit) and not the treatment-related frequencies. But still atrial fibrillation, with a frequency 2,7% vs 1.6% in the PBO group, are neither above 5% nor occurring in >2% than in the PBO group.

Serious adverse events and deaths, other significant events

Deaths

In study 301, 7 patients in placebo arm (0.8%) and 6 patients in LEC10 BW arm (0.7%) had a TEAE leading to death. None of the deaths were considered related to study treatment. Each PT occurred only in 1 patient in each treatment group, and it is recognised that frequency and cause of death were similar in both treatment arms.

In addition, the applicant reported 2 other highly publicized cases of death that occurred after the DCO April 2022. Both of these deaths were due to a macrohaemorrhage event. One patient appeared to have a distal left middle cerebral artery occlusion after 1 month of starting lecanemab therapy in Study 301 OLE Phase following treatment with placebo in study Core and was treated with tPA. The patient had bilateral cerebral haemorrhage 8 minutes after tPA infusion and died several days later. The autopsy showed "extensive multifocal intraparenchymal haemorrhages, cerebral amyloid angiopathy (CAA), "high" AD neuropathologic changes, and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within the blood-vessel walls". Although the investigator classified the event of cerebrovascular accident to be not related to study drug, the event of cerebral haemorrhage was classified to be related to study drug.

In addition, the publication by Castellani *et al*. (2024) which reported on the event states that "the neuropathological examination in this case indicates the presence of a robust phagocytic response to anti-Aβ therapy that extends beyond protofibrils and includes phagocytosis of insoluble Aβ aggregates of CAA" suggesting that the action of lecanemab could be implicated in the haemorrhagic event. In addition, Reish et al. (NEJM, 2023) suggest that the extensive number and variation in sizes of the cerebral haemorrhages in this patient would be unusual as a complication of t-PA solely related to cerebrovascular amyloid.

Therefore, although the applicant considered the event as not related to the study medication based on the fact that "there have been reports of fatal large catastrophic intracerebral haemorrhages after tPA administration in patients with CAA in the absence of anti-amyloid therapy, and considering that there have been reports in the literature of vasculitis associated with cerebral amyloid angiopathy in the absence of anti-amyloid therapy", the timing of the event do not allow to rule out a relation with lecanemab.

This case illustrates the need for thrombolytics as acute treatment for potentially life-threatening conditions such as stroke, myocardial infarction, and pulmonary embolism. Indeed, conditions where initiation of thrombolytics and anticoagulant would be indicated, in an elderly population with high risk of CV events, are relatively common. The applicant proposed a warning recommending that "additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tPA) to a patient already being treated with lecanemab".

The second patient was receiving aspirin 81 mg and apixaban anticoagulation for atrial fibrillation. The subject received PBO in Study 301 Core and received the first dose of LEC10-BW in the OLE part. The last dose of LEC10-BW was received on [date removed]. The subject fell, and safety MRI on [date removed] showed left occipital macrohaemorrhage. Apixaban treatment was interrupted, and [date removed], the patient had a myocardial infarction treated with heparin bolus (later discontinued due to the intracerebral haemorrhage). The cause of death noted in the autopsy was "No cause of death was present within the brain. A terminal cardiopulmonary event is most probable." This case is confounded by the subject's concomitant use of apixaban and aspirin for ongoing atrial fibrillation and by the multiple falls preceding the cerebral haemorrhage.

A third case was also publicized, a patient homozygous APOE4 carrier, died following an emergency hospitalisation with neurological symptoms of sudden onset, including possible seizure, and with an extensive brain swelling and bleeding. Similarly to the case described above in the patient who received tPA, the patient received lecanemab in OLE part after having received placebo in Core study 301 and had cerebral symptoms compatible with an acute stroke after the 3rd dose of lecanemab but was determined not to be a candidate for tPA. The subject was started on aspirin, levetiracetam and empirical antibiotics and was started on IV heparin for AF. An MRI was performed 2 days after the start of the event and showed hemosiderin stain and extensive areas of low-attenuation which could represent oedema. The central reader of study 301 who analysed these MRI images reported severe ARIA-E and 51 microhaemorrhages. IV heparin was discontinued and solumedrol was started. Following discussion with the family which confirm the subject's living will of do-not-resuscitate status, the patient was extubated. The patient passed away 5 days after the start of the event. After an autopsy, the cause of death was determined as atherosclerotic and hypertensive heart disease with a contribution of acute respiratory distress syndrome. Neuropathological findings included in addition to AD neuropathological change, CAA related inflammation and moderate to severe small vessel ischemic disease. Furthermore, "the microscopic sections revealed the gross petechial haemorrhages were due to acute cerebral vasculitis", consistent with ARIA, and which is attributed to the lecanemab treatment and consistent also with CAA. A second review was consistent with the first one with the conclusion that "the pathologic findings and the clinical history suggest that lecanemab may have exacerbated the underlying CAA, leading to many haemorrhages and ultimately to death." Although the applicant

reminded that the initial autopsy concludes to a cardiovascular cause of death, the second neuropathology concludes to a contribution of lecanemab by exacerbation of CAA. This, together with the temporality of the initial event following the 3rd dose of lecanemab suggest that a role of lecanemab cannot be excluded regarding the cause of death and that at least lecanemab is possibly involved in the exacerbation of the CAA.

Overall, in the three above mentioned deaths, although confounding factors may impair the analysis, the contribution of lecanemab cannot be excluded.

Additional analysis of haemorrhagic events in patient who received concomitant anti-thrombotic medication were provided. Analyses showed that although incidences of haemorrhagic events were similar in both LEC10-BW and placebo groups in patients who received overall antithrombotic medication, haemorrhages were more frequent in LEC10-BW arm than in placebo arm in patients who received concomitant antiplatelet therapy.

In Pool Core, deaths were consistent with data of both Study Cores 201 and 301.

Only one death was deemed possibly related to study drug by investigators (study 201, LEC2.5BW), this death was due to brain neoplasm (high-grade infiltrating astrocytic neoplasm, indicating the diagnosis of glioblastoma). The death was deemed possibly related to study drug by investigators. The Applicant clarified that in the lecanemab programme this case is the only neoplastic lesion of the central nervous system of primary origin. The applicant considered this case as an incidental finding, reflecting the incidence rates of GBM in the aged population. Further the applicant elucidated that the complete evaluation of potential for carcinogenicity has concluded a lack of genotoxicity, no plausible link between mechanism of action and carcinogenesis, no histopathology signals in a chronic toxicology study, and no evidence of immunosuppression (in both nonclinical and clinical studies).

Following an update of safety data at DCO Dec 2022, the applicant declared that 6 additional deaths occurred in study 301 OLE, between DCO April 2022 and Dec 2022, of which 4 were considered possibly related to study treatment. On these 4 deaths considered possibly related to study treatment, 3 patients had concurrent risk factors (i.e., CAA, anticoagulant or thrombolytic treatment).

Serious Adverse events

In study 301, treatment emergent SAEs occurred at higher frequency in LEC10 BW arm (14.0%) than in placebo arm (11.3%). This imbalanced was mainly due to a higher incidence of serious IRR (1.2%) and ARIA-E (0.8%) in LEC10 BW arm compared to placebo arm (none).

Within the Cardiac Disorders (SOC), SAEs occurred at rates of 1.0% in PBO and 2.1% in LEC10-BW and the most commonly reported were atrial fibrillation (PBO 0.3%; LEC10-BW 0.7%) and angina pectoris (PBO 0%; LEC10-BW 0.7%). SAEs of syncope also occurred more often in the LEC10-BW (PBO 0.1%; LEC10-BW 0.7%).

Incidences of serious events in Pool LEC10 BW were consistent with incidences observed in study 301 and 201.

Adverse Event of Special Interest

ARIA-E, ARIA-H (cerebral microhaemorrhages, superficial siderosis, macrohaemorrhage), infusion-related reactions, skin rash, other hypersensitivity, suicidal ideation and suicidal behaviour were considered AESI as per study 301 protocol.

- **Infusion-related reactions**

In study 301 Core, the incidence of IRRs was higher in LEC10 BW (26%, 237/898 patients) than in placebo arm (7.4%, 66/897 patients) and were most of the time of low grade, with 227/237 patients in LEC10 BW arm and all patients in placebo arm who experienced a grade 1/2 event. IRR occurred mainly following first administration with a decreasing incidence over time. All serious but one event resolved within 4 days, the reminder resolved with 7 days. Overall, data from study 201 were consistent with study 301 and suggests also that the severity of IRR increased with the dose.

No patients received premedication before the first lecanemab infusion. Most IRR occurred at first infusion (75%). In total 237 LEC10-BW subjects had IRR, hereof 78 subjects had a Grade 1 IRR, and 144 of the IRR were grade 2. Of the 237 LEC10-BW subjects that experienced an IRR 44% received a pre-treatment for the next infusion. For subjects with Grade 1 and 2 IRRs, the use of premedication for subsequent infusions did not appear to change the likelihood of having a subsequent IRR. The applicant has provided an acceptable precaution regarding IRR. Based on the above and the provided precaution it is acceptable that premedication is not required with the first dose.

The majority of IRR were mild to moderate. A 1-hour infusion is proposed and is consistent with the infusion-rate in study 301. It is acceptable that an even slower infusion-rate is not needed for first infusions, taken into account the mostly rather mild/moderate IRR and the proposed precautions related to IRR.

The majority of IRRs occurred on the same day as the infusion. Most severe IRR (5 out of 6, data from the last missing) occurred during the infusion or within approximately 2.5 hours after infusion completion. As infusion reaction occurred up to 2.5 hours after the infusion, the applicant agreed to include a 2.5-hour observation time after the first infusion in the product information, as relevant.

In Study 301 Core a total of 19 hypersensitivity events (1 PBO, 18 LEC10-BW) occurred more than 24 hours after the last dose. All of these events were mild or moderate in severity, with the most common symptoms being rhinorrhoea, rash, and headache. Delayed hypersensitivity has been accepted as adverse event, but the symptoms of delayed hypersensitivity reaction (rhinorrhoea, rash, headache, rhinitis and hair loss) should also be added. There were no delayed cases of anaphylaxis.

- **Amyloid-related imaging abnormalities-oedema/effusion**

In study 301, the incidence of ARIA-E was higher in LEC10 BW (12.6%, 113/898 patients) than in placebo arm (1.7%, 15/897 patients). On the 113 events in LEC10 BW arm, 73 were concurrent with an ARIA-H event (65%). In LEC10 BW arm, the incidence of ARIA-E increased with the number of *APOE4* alleles. While most ARIA-E events occurred within the first 3 months in LEC10 BW arm, they were randomly distributed in placebo arm. Overall, characteristics of isolated ARIA-E events were consistent with ARIA-E event that co-occurred with ARIA-H.

Although ARIA-E events were mostly asymptomatic, symptoms (mainly headache, confusional state, dizziness, and nausea) occurred in 20% of patients who experienced ARIA-E (none in placebo arm). These are overall symptoms that occur very often as TEAEs.

In Study 301 the rates of confusional state and dizziness were very similar in LEC10-BW and PBO. Whereas nausea and headache occurred more often in LEC1-BW than PBO (headache: PBO 8.1%, LEC10-BW 11.1% and nausea PBO 2.8%, LEC10-BW 3.5%). The applicant does not consider that reported events of headache, confusional state, dizziness, or nausea is necessarily indicative of mild ARIA. Nevertheless, the applicant considered the adverse event of nausea related to lecanemab, with the frequency Common. In patients receiving LEC10 BW, radiographic severity was mild and moderate in majority with 32.7% and 58.4% of patients who experienced an ARIA-E respectively.

Although the impact of *APOE4* status on seriousness is unclear due to the low number of patients who experienced serious events (0.8% of patients in LEC10 BW arm, 6% of ARIA-E events), the severity of ARIA-E increased with the number of *APOE4* alleles.

All events of ARIA-E in LEC10 BW resolved, with the majority (81%) resolving within 4 months. Two third of patients had dose interruption and time to resolution was similar whether the treatment was interrupted or not.

Most patients experienced only one ARIA-E event although 1/4 of patients (28/113) experienced a second event. Additional occurrences were rare with one patient experiencing 4 events of ARIA-E. As some symptoms of ARIA could be hidden by symptoms of AD such as confusional state, the applicant provided an analysis of relevant adverse events (headache, confusional state, dizziness, nausea) in subjects with and without ARIA and proposed to perform a clinical evaluation included an MRI if indicated in case a patient experiences symptoms suggestive of ARIA.

Overall, ARIA-E events occurred at a very common frequency, were mainly asymptomatic and of mild and moderate severity. Data suggest moreover that recurrence of ARIA-E increase with the number of APOE4 alleles, which is consistent with the fact that the risk of ARIA increase with the number of APOE4 alleles.

The Applicant proposed a close monitoring with a MRI prior the 5th, 7th, and 14th dose, considering 92% of ARIA-E occurred at this time point during the pivotal study 301. The applicant agreed to shorten the 1-year frame for collection of pretreatment/historical MRI to 6 months which is considered more suitable, considering the high concerns of the ARIA events, and the need to identify patients at increased risk of cerebral haemorrhage such as CAA or other lesions (aneurysm, vascular malformation).

In study 201, analysis of ARIA-E is impaired by 1) different stopping rules which were more stringent than in study 201, and 2) by lower rates of patients APOE4 carriers in LEC10 BW. However, results were overall similar to study 301.

In total 44 subjects with radiographically mild asymptomatic ARIA-E continued dosing. The majority of these subjects (73%) ARIA-E radiographic severity did not worsen and resolved spontaneously. For the remaining 27% the ARIA-E became radiographically moderate and resulted in dose interruptions later on, after which the ARIA-E resolved radiographically.

Finally, besides the data submitted in this Application, the systematic review by Alves et al., (Neurology 2023) suggests that anti- β-amyloid drugs may be associated with an acceleration of brain atrophy. More specifically, the treatment with anti-β-amyloid monoclonal antibodies may be associated with an increase in ventricular enlargement and the results suggested furthermore that the enlargement of ventricles was strongly correlated with the frequency of ARIA-E. While the applicant's comments to this article are acknowledged, including the possibility that the phenomenon is a pseudo-atrophy due to mobilisation of amyloid and reduced gliosis, substantial uncertainties remain on how this phenomenon might translate into clinical consequences in the long term.

Based on data from study 201 the incidence of ARIA-E seems to be dose dependent and occurs with a greater incidence at higher doses. As discussed in the PK section high weight patients have a higher exposure, and a slightly higher risk of ARIA-E.

- **Amyloid-related imaging abnormality-haemorrhage**

Incidence of ARIA-H events *(*"microhaemorrhage and hemosiderin deposit", "superficial siderosis" and "macrohaemorrhage"), was higher in LEC10 BW arm (17.3%) than in placebo arm (9.0%) and increased with the number of *APOE4* alleles from 11.6% in *APOE4* non carriers to 39.0% among homozygote *APOE4* carriers in LEC10 BW arm. Most cases of ARIA-H were ongoing at the end of Study

301 Core and all cases of macrohaemorrhage were ongoing. Thus, a mandatory *APOE4* assessment prior to lecanemab administration was proposed during the procedure. In the same line, the SAG-N experts agreed by consensus that there should be a contraindication for homozygous ApoE4 carriers.

Cerebral microhaemorrhage was the PT with the highest incidence among PTs of ARIA-H and with the highest difference between both treatment arms with 14% in LEC10 BW arm and 7.6 % in placebo arm. Microhaemorrhage ≤ 10 (13.3% in LEC10 BW arm and 7.6% in placebo arm) were more frequent than microhaemorrhage >10 (3.0% in LEC10 BW arm and 0.1% in placebo arm).

Although most treatment emergent ARIA-H were radiographically mild or moderate, 20% of the reported ARIA-H were graded as severe, mostly microhaemorrhages that resulted in a cumulative number greater than 10 microhaemorrhages. In addition, although most events were asymptomatic (142/155 in LEC10 BW arm and 79/81 in placebo arm), 8.4% of patients who experienced an ARIA-H event in LEC10 BW arm had symptoms.

Serious ARIA-H occurred at an incidence of 0.6% (5/898) in LEC10 BW arm and 0.1% (1/897) in placebo arm and were mostly related to cerebral haemorrhage. Half of the cases were concurrent with ARIA-E and half of the cases occurred in *APOE4* non carriers.

Recommendations for management of ARIA-H and ARIA-E in section 4.2 of the proposed SmPC as routine measures were acknowledged. The applicant modified the recommendation of treatment regarding patients who develop intracerebral haemorrhage greater than 1 cm in diameter, as requested. In the latest proposed SmPC lecanemab is recommended to be permanently discontinued if intracerebral haemorrhage greater than 1 cm in diameter occurs.

In addition, ARIA-H stabilized more slowly in LEC10-BW arm than in placebo arm, with 11.1% and 23.7% of non-stabilized ARIA-H at first follow up MRI in placebo and LEC10-BW arm respectively. After that, the kinetics of stabilisation seems similar. To be noted, according to APOE4 status, there is 40% of non-stabilized events at first follow-up MRI in patients with homozygous APOE4 status in LEC10-BW (vs 16.1% in non-carriers).

Overall, the impact of ARIA-E and H events on the cognitive status of the patients is questioned. An analysis on the cognitive status of each patient before and after ARIA events along with a discussion including the impact of multiple ARIA events was provided. Although this analysis did not suggest any short-term impact on the cognitive status, long term impact remain to be uncertain.

An infrequent but worrisome symptom of ARIA is seizures of different types. In Study 301 Core, there were 9 patients (PBO 4; LEC10BW 5) with TEAEs or symptoms related to ARIA in SMQ of convulsions. Incidence of TEAEs in SMQ of convulsion (i.e., seizures) not associated with ARIA-E or ARIA-H events were infrequent and similar between treatment groups (PBO 3/897 [0.3%], LEC10-BW 2/898 [0.3%]). The exposure adjusted rate for PBO was 0.002 per patient year and 0.002 per patient year for LEC10-BW. Incidence of TEAEs in SMQ of convulsion (i.e., seizures) associated with ARIA-E or ARIA-H events, were 1/897 [0.1%] for PBO and 3/898 [0.3%]) for LEC10-BW. The exposure adjusted rate for PBO was 0.001 per patient year and 0.003 per patient year for LEC10-BW. In Study 301 Core and OLE (cutoff date of 01 Dec 2022), when adjusted to patient years of exposure, the rate is 0.003 per patient year.

Incidences of ARIA-H were similar within subgroups of patients with or without anti-thrombotic therapy. However, further analysis showed a difference of haemorrhages between both treatment groups in patients receiving antiplatelets agents.

Laboratory findings, vital signs, physical findings and other observations related to safety

In study 301 and study 201, baseline chemistry values were within normal ranges and no clinically meaningful changes over time were observed.

Markedly abnormal low calcium occurred more often in the lecanemab arm (1.8%) than in the PBO arm (0.9%). Also, in study 201 more patients receiving lecanemab had markedly abnormal low calcium than patients receiving PBO (though without increased incidence with increasing dose). However, the numbers of calcium imbalance are small. Further the applicant elucidates that all cases of abnormal low calcium resolved, and no subjects had multiple events. Based also on the mechanism of action, it is acceptable that the higher incidence of markedly abnormal low calcium is a chance finding and not related to lecanemab treatment. In study 301 baseline haematology values were within normal ranges and no clinically meaningful changes over time were observed.

In study 301 and 201 Core, a slight trend of higher incidence of clinically notable high temperature was observed in LEC10 BW arm (0.7%) compared to placebo arm (0%). These events were observed only post dose, it is acknowledged that it can be considered to be part of infusion-related reactions.

Overall, in subjects with EAD in study 301 and 201 Core, it is acknowledged that suicidal ideation of various grades (C-SSRS) was similar between lecanemab and placebo arms although there was one event of suicidal attempt in LEC10 BW arm in study 301.

Safety in special population

The applicant provided an analysis of special population by age, race, APOE carriers (non-carriers, heterozygous, homozygous) and clinical subcategories (MCI and mild AD), region, and use of AD symptomatic medication. The most noteworthy finding is the increased risk in APOE4 homozygotes (see data above).

Immunological events

At baseline, the prevalence rate of ADA was similar and around 5% in both treatment arms and the prevalence rate of Nab was 0.3% and 0.2% in placebo and LEC10 BW arm respectively, with generally low titres.

The applicant provided additional tables and discussions regarding the impact of ADA on safety and the reliability of the results. Overall, the provided data are not suggestive of an impact of ADA on immunogenicity related TEAEs.

In Study 201 Core, the incidence of treatment-emergent positive ADA in LEC10-BW was much higher than in study 301 (40.9%), also incidence of NAb was much higher in study 201. In study 301, 45.9% (406/884) subjects were ADA negative inconclusive. The discrepancies observed are likely due to differences in sensitivity and specificity.

Discontinuation due to adverse events

In study 301 Core, the incidence of TEAEs leading to treatment discontinuation was similar in LEC10 BW (3.1%) arm and in placebo arm (2.9%).

In study 301 Core the incidence of TEAEs leading to study drug interruption was higher in LEC10-BW arm (19.5%) than in placebo arm (7.9%). This difference was mostly due to events of ARIA-E, ARIA-H (microhaemorrhage).

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of lecanemab is driven by IRR, ARIA-H and ARIA-E. While IRR were mainly of low grade, except for an anaphylactic reaction, and with standardized management, ARIA-E and H are events which remain to be fully characterised, with uncertain long-term consequences. Although the majority of events were of mild or moderate severity, serious events occurred, including intracerebral haemorrhages. These events cannot be prevented nor mitigated but only monitored. The applicant has

not demonstrated that any of the proposed risk-minimisation measures sufficiently addresses the issues identified.

2.7. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

Not applicable.

2.9. Product information

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and functional decline, and the main cause of dementia. AD is ultimately fatal.

According to the World Alzheimer Report 2018 more than 50 million people worldwide are living with dementia, and in the European population the prevalence of AD is estimated at 5.05 (Niu, 2017). According to a review in US, the prevalence of MCI is estimated around 8-10% for adults aged 60-69 years, 15% for adults aged 70-79%, and 25% for elderly aged 80-84 years (Perterson, 2018).

The claimed indication was initially: a disease modifying treatment in adult patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease (early Alzheimer's disease). It is to note that the presence of amyloid beta (Aβ) pathology must be confirmed via an appropriate test prior to initiating treatment. During the procedure, the applicant modified the indication targeted as

follows: the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (early Alzheimer's disease) in adult patients with confirmed amyloid pathology.

3.1.1. Available therapies and unmet medical need

Currently, pharmacological treatment approved in Europe (i.e. cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine) are targeted toward symptomatic therapy only.

There are no therapies approved that modify the course of the clinical disease progression at any stage of the disease.

Overall, there is a need for disease modifying therapies.

3.1.2. Main clinical studies

The main evidence of efficacy is based on a single Phase 3 study, BAN2401-G000-301 (Study 301), a global, multicentre, double-blind, placebo-controlled, parallel-group study in subjects with EAD that evaluated LEC10-BW for 18 months to confirm the safety and efficacy of lecanemab. The core phase was followed by an open label phase (Open-label Extension (OLE)) evaluating a dose of LEC10-BW in all subjects.

3.2. Favourable effects

The analysis for the primary endpoints of the pivotal study showed a statistically significant difference of -0.451 (95%CI: -0.669, -0.233; p=0.00005) between lecanemab and placebo in change from baseline in CDR-SB at 18 months.

Additionally, the 3 key clinical endpoints shown a statistically significant difference in favour of lecanemab versus placebo: -1.442 (95%CI: -2.270, -0.613; p=0.00065) in change from baseline in ADAS-Cog14 at 18 months, -0.050 (95%CI: -0.074, -0.027; p=0.00002) in change from baseline in ADACOMS at 18 months, and 0.797 (95%CI: 0.274, 1.321; p=0.00284) in change from baseline in ADCS MCI-ADL at 18 months.

Regarding the pharmacodynamics, the first key secondary endpoint, change from baseline in amyloid PET using centiloids, showed a decrease in brain amyloid level over the study duration in the lecanemab arm (mean [SD] -56.8 [36.15] centiloids), while the level slightly increased in the placebo arm (mean [SD] 4.7 [12.82] centiloids). The difference is statistically significant.

3.3. Uncertainties and limitations about favourable effects

The confirmatory evidence comes from a single pivotal trial without replication of the results. Moreover, this need to be seen in the context of a Phase 2 dose finding study that did not meet its primary endpoint. The study has been powered to show a non-clinically relevant effect size (i.e. a difference of 0.337 in CDR-SB) mitigating the weight of the statistical significance of the primary result in the body of evidence.

The size of the effect in the primary analysis (-0.451 in change from baseline in CDR-SB at 18 months) is considered small. A more conservative handling of missing data led to a lower estimate of the effect (-0.401), and additional sensitivity analyses show that the effect ranges between 0.23 and 0.47 with the worst- and best-case scenarios of missing data for the primary analysis of CDR-SB changes over 18 months. A benefit deriving from a difference in CDR-SB < 0.5 points is small and, in the context of

a single pivotal trial, results are expected to be particularly compelling with respect to clinical relevance, and not only statistical significance. The SAG-N experts considered by consensus that the above-mentioned observed differences in favour of Leqembi are not clinically relevant and meaningful for the patients. The SAG-N experts noted that the minimally clinically important differences (MCID) for CDR-SB are 1 point and between 1 and 1-2 points for mild cognitive impairment (MCI) due to Alzheimer Disease (AD) and mild AD, respectively. In this regard, the literature discussing the criteria to evaluate clinical relevance of between-groups differences as opposed to within-patient changes is acknowledged. However, in RCTs the between-groups difference can be assumed to correlate with the average difference between the same patient treated and untreated. Hence, the MCID represents, if not an automatic criterion, a quantity that can be considered to put results into context. Moreover, several progressor analyses based on various worsening cut-offs at the individual level were provided and showed modest differences at all thresholds of CDR-SB score. In any case, threshold analyses do not imply that the value chosen as threshold is the effect at the individual level, but merely that reaching a certain threshold happens at different times in groups separated by the average difference.

The experts of the SAG also highlighted a potential of functional unblinding due to the relatively large proportion of infusion-related AEs, which is particularly relevant in the case of a caregiver-informed primary outcome. This could have contributed to the observed difference between those in the Leqembi arm compared to the control group.

The results of the key clinical secondary endpoint are also limited, and do not provide further support demonstrating the efficacy of lecanemab. In particular, the difference versus placebo in change from baseline in ADAS-Cog14 at 18 months is below the minimal clinically important difference. The SAG-N also noted that the small difference in CDR-SB is in line with the small difference on key secondary outcomes. The key secondary endpoint ADCOMS is a non-validated endpoint.

There are concerns on the effect in the ApoE4 homozygous carriers, while this population is particularly at risk. Phase 3 study results suggest a reduced response in these patients compared to the heterozygous and non-carriers, and even a worse performance than in the placebo arm. Moreover, these results are contradictory with the applicant's PD hypothesis and the Phase 2 results.

The Phase 3 data do not allow to further relate the pharmacodynamics effects with relevant clinical outcomes, and questions whether amyloid burden reduction is truly associated with a clinical benefit. Only proof of mechanism has been established. The proof of concept has not been sufficiently shown from the non-clinical perspective as there is insufficient data to allow for a meaningful interpretation to humans and that assessment of functional efficacy should be traced back to clinical evidence. Additionally, the experts of the SAG noted the lack of association between the changes on pathology (B-amyloid load) and the changes in the cognitive function at the individual level. Overall, the concerns about long-term efficacy together with the poor correlation between brain amyloid load and clinical endpoints did not allow to establish the demonstration of disease modifying properties.

There are uncertainties on long term efficacy, with the limited data from the OLE period not clearly demonstrating that the treatment has an effect on the progression of the disease. The Applicant has not generated data suitable to inform on the necessary maintenance dose and dosing intervals beyond the removal of the cerebral amyloid plaques.

3.4. Unfavourable effects

The most frequent TEAEs, occurring in LEC10 BW arm were IRR (26.3%), ARIA-H microhaemorrhage and hemosiderin deposit (14.0%), ARIA-E (12.6%), headache (11.1%) and fall (10.4%). A difference compared to placebo was observed for IRR (7.1%), ARIA-H (7.7%), ARIA-E (1.7%) and headache (8.1%). Incidence of ARIA-H events ("microhaemorrhage and haemosiderin deposit", "superficial

siderosis" and "macrohaemorrhage"), was also higher in LEC10 BW arm (17.3%; 155/898) than in placebo arm (9.0%; 81/897).

Anxiety (4.2 vs 5.0%), fatigue (2.7 vs 4.1%), nausea (2.8 vs 3.5%), vomiting (2.5 vs 3.2%), rash (1.9 vs 3.2%), insomnia (2.3 vs 2.7%), atrial fibrillation (1.6 vs 2.7%), haematuria (0.8 vs 2.3%) and syncope (1.3 vs 2.0%) occurred more often in the lecanemab 10 BW arm. For atrial fibrillation, it is noted that there is a consistently higher incidence of atrial fibrillation across studies.

The safety profile of lecanemab is mainly characterized by ARIA-E and ARIA-H events. This is consistent with the known safety profile of others anti-β-amyloid monoclonal antibodies. In data submitted, ARIA-E and ARIA-H occurred at a very common frequency. Both type of ARIAs occurred isolated or concurrent with each other. Indeed, 65% of all ARIA-E events were concurrent with ARIA-H in LEC10 BW arm and 48% of all ARIA-H events in LEC10BW were concurrent with ARIA-E. While most ARIA event were asymptomatic, some associated with symptoms, including in rare cases seizures.

Most ARIA-E events occurred within the first 3 months in LEC10 BW arm, with the majority (81%) resolving within 4 months. Time to resolution was similar whether or not the treatment was interrupted.

Although ARIA-E events were mostly asymptomatic, symptoms (mainly headache, confusional state, dizziness, and nausea) occurred in 20% of patients who experienced ARIA-E (none in placebo arm). In patients receiving LEC10 BW, radiographic severity was mild and moderate in majority with 32.7% and 58.4% of patients who experienced an ARIA-E respectively, and with 8.0% of patients graded as severe. The incidence and severity of ARIA-E increased with the number of *APOE4* alleles. Serious events occurred in 0.8% of patients in LEC10 BW arm (thus, 6% of ARIA-E events).

Risk of ARIA-E and ARIA-H are very high in APOE4 carriers, especially in homozygote patients. Up to 33% of the ApoE4 homozygous patients (1 in 3 patients treated) experiencing ARIA-E and related monitoring burden due to treatment compared to 3.8% of untreated ApoE4 homozygous patients. The incidence of symptomatic ARIA-E and ARIA-H were noticeable in APOE4 homozygotes (9.2% and 3.5% respectively). ARIA related AEs leading to withdrawal is 10,6% in the same population if treated by lecanemab. In addition, it seems that high body weight patients (due to higher exposure) that are APOE4 non-carriers are also at higher hazard of ARIA.

Most patients experienced only one ARIA-E event although 1/4 of patients (28/113) experienced a second event. Additional occurrences were rare with one patient experiencing 4 events of ARIA-E.

As ARIA-E event cannot be predicted, nor mitigated, only a monitoring was proposed in the SmPC. The proposed recommended monitoring is a baseline (within one year) brain magnetic resonance imaging (MRI), then prior to the 5th, 7th and 14th infusions. Considering the high concerns on ARIA events, but also considering notably the case of a deceased patient with concurrent CAA (although it was an exclusion criteria), but also for excluding other concomitant medical disease (tumour, stroke, white matter lesions, bleedings) and to be able to monitor the count and size of existing lesions, the applicant agreed to shortened from 1 year to 6 months the maximum interval between last MRI and initiation of treatment with lecanemab.

Severe ARIA-H (severe ARIA-H microhaemorrhage is defined as ≥ 10 new incident microhaemorrhages and ARIA-H superficial siderosis >2 areas of superficial siderosis) was observed in 32/155 (20.6%) driven by ARIA-H microhaemorrhages. Symptomatic ARIA-H was observed in 13/155 (8.4%).

The onset time and distributions, of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E while isolated ARIA-H occurred throughout the course of treatment. ARIA-H stabilized more slowly in LEC10-BW arm than in placebo arm, with 11.1% and 23.7% of non-stabilized ARIA-H at first follow up MRI in placebo and LEC10-BW arm respectively. Then the kinetics of stabilisation seem similar. The incidence

of ARIA-H events increased with the number of *APOE4* alleles from 11.6% in *APOE4* non carriers to 38.0% among homozygote APOE4 carriers in LEC10 BW arm.

Cerebral microhaemorrhage was the PT with the highest incidence among PTs of ARIA-H and with the highest difference between the treatment arms with 14% in LEC10 BW arm and 7.6 % in placebo arm. Microhaemorrhage ≤ 10 (13.3% in LEC10 BW arm and 7.6% in placebo arm) were more frequent than microhaemorrhage >10 (3.0% in LEC10 BW arm and 0.1% in placebo arm).

Although most treatment emergent ARIA-H were radiographically mild or moderate, 20.6% of the reported ARIA-H were graded as severe, mostly microhaemorrhages that resulted in a cumulative number greater than 10 microhaemorrhages. In addition, although most events were asymptomatic, 8.4% of patients who experienced an ARIA-H event in LEC10 BW arm had symptoms.

Most cases of ARIA-H with PBO or LEC10-BW were ongoing at the end of both Study 301 Core and Study 201 Core. All cases of macrohaemorrhage with PBO or LEC10-BW (in either study) were ongoing, which was expected, as these events tend not to resolve, but at best stabilize.

Serious ARIA-H occurred at an incidence of 0.6% and 0.1% in the LEC10 BW and placebo arms, respectively (3% [5/155] and 1,2% [1/81] of ARIA-H events) and were mostly related to cerebral haemorrhage. Half of the cases occurred in APOE4 carriers.

ARIA-E was observed in 13% (113/898) of patients treated with lecanemab, of which 85% (96/113) continued on lecanemab treatment with or without dose interruption. Among those that continued lecanemab, 29% (28/96) experienced a recurrence of ARIA-E.

ARIA-H (with or without concurrent ARIA-E) was observed in 17% (152/898) of patients treated with lecanemab and 9% (80/897) of patients on placebo, of which 82% (125/152) and 80% (64/80) continued treatment respectively with or without dose interruption. Among those that continued, 46% (57/125) of patients treated with lecanemab and 38% (24/64) of patients on placebo experienced a recurrence of ARIA-H.

Additionally, in the TEAEs list of SOC terms more cardiac events occurred in the LEC10 BW arm than in the placebo (6.8% vs 9.5%). Parts of this is explained by atrial fibrillation (1.6% vs 2.7%). The remaining differences are driven by atrioventricular block first degree (0.4 vs 0.9%), bundle branch block left (0.3 vs 0.9%), sinus bradycardia (0.3 vs 0.8%) and angina pectoris (0,3% vs 1%) all occurred more often in the LEC10 BW. In addition, also prolonged QT occurred in 6 (0.7%) in the LEC10 BW vs 0 in the placebo arm. Noted is also that syncope occurs more often in LEC10-BW (2%) vs PBO (1.3%). Based on the low rates of cardiovascular events, the applicant proposes no risk minimisation, which is not endorsed. However, since the incidences of cardiac events points in opposite directions between the studies it can be accepted that angina pectoris, syncope, and QT prolongation in the LEC10 BW arm in study 301 may be due to chance alone, are not considered ADRs. Nevertheless, a certain level of uncertainty remains since observations in the pivotal study 301 might be more accurate than observations in study 201 due to a much higher number of patients.

In addition, the safety profile of lecanemab is also marked by a very common frequency of IRR in LEC10 BW (26%), which were most of the time of low grade. IRR occurred mainly following first administration with a decreasing incidence over time. All serious but one event resolved within 4 days, the other resolved within 7 days.

3.5. Uncertainties and limitations about unfavourable effects

The long-term consequences of ARIA events remain uncertain, despite the analyses provided by the applicant partially attenuate the concern of a consistent negative effect on cognition in the first 18

months of treatment. The recent report of a detrimental effect of anti-β amyloid antibodies on the brain volume associated with the frequency of ARIA-E is also of concern, while its translation into clinically meaningful consequences is unclear. Even within the limited duration of the studies reported, ARIA re-occurred in several patients. For LEC10-BW, 87.3% (69/79) subjects received recurrent treatment. More than half of subjects (56.5%, 39/69) had additional treatment-emergent ARIA-E or ARIA-H (microhaemorrhage or superficial siderosis) after recurrent treatment; while most of these re-occurrences did not lead to discontinuation, the longer-term cumulative effects are unknown.

An important concern is that real world ARIA occurrences and consequences may be more severe if, in some settings, there are challenges to the full implementation of the risk-minimisation measures proposed (especially the monitoring MRIs), if the patient population treated presents more comorbidities than the trial population, and if clinicians are less expert than those who participated in the randomized trial.

The death of a patient following tPA treatment for a cerebral artery occlusion raises the question of the safety of thrombolysis in lecanemab treated patients, and the proposed additional warning for patients receiving concomitant anti-thrombotic and thrombolytic medication is not sufficient.

3.6. Effects Table

Table 55. Effects table for lecanemab for early AD

Effect	Short Description	Unit	Treatment LEC10-BW n=898	Control Placebo N=897	Uncertainties/ Strength of evidence	References
Favourable Effects						
CDR-SB	Change from baseline in the CDR-SB at 18 months	Adjusted mean (SE)	1.213 (0.082)	1.663 (0.080)	The effect is of small magnitude	Study 301 CSR - ITT
Unfavourable Effects						
ARIA-E	Incidence	%	12.6	1.7	Clinical consequences variable and – in the long term – not fully characterised	Safety dataset
ARIA-H	Incidence	%	17.3	9.0	Clinical consequences variable and – in the long term – not fully characterised	Safety dataset
Intracerebral haemorrhage	Incidence	N	6	1		Study 301 Core
Seizures associated with ARIA	Incidence per patient-year		0.003	0.001		Safety dataset

Abbreviations: ARIA-E: amyloid related imaging abnormality-oedema/effusion, ARIA-H: amyloid related imaging abnormality-microhaemorrhages and hemosiderin deposits
Notes: ARIA-H incidence provided in this table includes microhaemorrhage, superficial siderosis and macrohaemorrhage)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The confirmatory evidence comes from a single pivotal without replication of the results, in the context of a failed Phase 2 dose finding study which did not met its primary endpoint.

While statistically significant, the observed effects in the main clinical outcomes are considered small. The differences versus placebo are below the assumed minimal clinically important change in CDR-SB, the primary endpoint, and in ADAS-Cog14, the first key clinical endpoint. Moreover, although the statistically significance of the primary endpoint is acknowledged, it is highlighted that the study has been powered to show a very small effect size, mitigating the strength of the results. Importantly, the SAG experts *considered by consensus that the observed differences in favour of Leqembi are not clinically relevant and meaningful for the patients*.

Additionally, the Phase 2 and Phase 3 results does not allow to relate the pharmacodynamic effects to relevant clinical outcomes, and question whether amyloid burden reduction is truly associated with a clinical benefit. A poor correlation between change from baseline in amyloid PET using centiloids and change from baseline in main clinical endpoints was observed. Moreover, these concerns are also supported by non-convincing PK/PD outcomes. Only proof of mechanism has been established. The

proof of concept has not been sufficiently shown. Moreover, the experts of the SAG-N *noted the lack of association between the changes on pathology (B-amyloid load) and the changes in the cognitive function at the individual level.*

It should also be stressed that the concerns about long-term efficacy together with the poor correlation between brain amyloid load and clinical endpoints did not allow to establish the demonstration of disease modifying properties. A strong concern is also the observed effect size in the ApoE4 carriers, as this population is particularly at risk for AD. The Phase 3 study results points to an even smaller effect size in the homozygous ApoE4 carriers compared to non-carriers. This is even more puzzling given the hypothesis of the applicant on the mechanism of action which should be more suited to ApoE4 carriers.

The strong concerns about a small benefit of lecanemab for the patients with EAD need to be balanced against the safety concerns identified.

Overall, the most important safety concerns regarding the safety profile of lecanemab is the frequent occurrence of ARIA events. Although events were mostly asymptomatic and of low grade, serious events occurred, including cerebral macrohaemorrhages and seizures.

Events of ARIA-E and ARIA-H were very commonly observed in the overall population and even more so in the APOE4 carriers, especially in homozygous patients. In the overall population, 20.6% of the ARIA-H events were severe, 8.4% of the ARIA-H events were symptomatic and 3% were serious. Also, the incidence of symptomatic ARIA-E and ARIA-H were noticeable in APOE4 homozygotes (9.2% and 3.5% respectively). Most cases of ARIA-H were ongoing at the end of the study. ARIA related AEs leading to withdrawal is 10,6% in the same population if treated by lecanemab. The occurrence of these events was higher in the lecanemab group as compared to placebo. Following an initial event of ARIA, the rate of recurrence on resumption of treatment with lecanemab is very common.

An important concern is that real world ARIA occurrences and consequences may be more severe if, in some settings, there are challenges to the full implementation of the risk-minimisation measures proposed (especially the monitoring MRIs), if the patient population treated presents more comorbidities than the trial population, and if clinicians are less expert than those who participated in the randomized trial.

The death of a patient following tPA treatment for a cerebral artery occlusion raises the question of the loss of chance of getting effective emergency treatment vs increased risk of ARIA-H. This concern was also raised by the SAG-N experts.

In addition, the CHMP early contact with patient and consumer organisations, stated that *"ARIA were perceived as scary and worrying"*. In particular, patients who have a good quality of life may not accept any life threatening or very serious side effects.

While all events of ARIA-E resolved in the pivotal study, a recent review suggests a detrimental effect of anti-βamyloid antibodies on the brain volume associated with the frequency of ARIA-E. In addition, information on stabilisation on the ARIA-H events are lacking, thus uncertainties remain with regards to the long-term impact of these events.

3.7.2. Balance of benefits and risks

Overall, the benefit-risk balance of lecanemab is negative. All available evidence has been evaluated and having considered the magnitude of the benefits and risks, and the associated uncertainties, the CHMP considers that the effect size observed in main clinical outcomes is small, with a diminished response in ApoE4 homozygous carriers, and the safety of lecanemab is not sufficiently demonstrated.

Lecanemab treatment causes amyloid-related imaging abnormalities (ARIA) in a significant proportion of treated patients. Clinical consequences may be serious in some patients and may include seizures and intracerebral haemorrhage; Notably, this risk is particularly pronounced in apolipoprotein E ε4 (ApoE ε4) homozygote carriers.

3.7.3. Additional considerations on the benefit-risk balance

3.7.3.1 SAG-Neurology (SAG-N) answers to CHMP questions for Leqembi

1. The difference in CDR-SB is estimated between -0.40 (95%CI: -0.62, -0.18) and -0.45 (95%CI: -0.67, -0.23) (nb: a more conservative estimation has been requested, but not yet provided). Does the SAG consider such a difference to be clinically relevant and meaningful for the early AD patient (MCI due to AD and mild AD)?

The SAG-N experts considered by consensus that the above-mentioned observed differences in favour of Leqembi are not clinically relevant and meaningful for the patients. The SAG-N experts noted that the minimally clinically important differences (MCID) for CDR-SB are 1 point and between 1 and 1-2 points for mild cognitive impairment (MCI) due to Alzheimer Disease (AD) and mild AD, respectively[1] .

The SAG-N experts made some additional comments. It was noted that the small difference in CDR-SB is in line with the small difference on key secondary outcomes, including ADAS-Cog, for which the MCID is around 3-4 points (Molnar FJ, JAGS 2009), whereas the difference between the Leqembi group and the placebo group was 1.44 points. It was also noted that it is likely that the difference in favour Leqembi is partly the result of selective drop-out of those doing worse in the intervention arm due to ARIA or other adverse events. This is supported by the additional more conservative analysis ('worst case scenario') requested by EMA with imputation of the worst outcome in those who dropped out, which resulted in a smaller difference between the groups of 0.25-point CDR-SB. Furthermore, the potential of functional unblinding due to the relatively large proportion of infusion-related AEs was highlighted, which is particularly relevant in the case of a caregiver-informed primary outcome. This could have contributed to the observed difference between those in the Leqembi arm compared to the control group. In line with other studies, the experts noted the lack of association between the changes on pathology (B-amyloid load) and the changes in the cognitive function at the individual level. The experts confirmed that it is appropriate to use the MCID threshold to inform clinical relevance at a trial level, as is common in clinical trials in slowly progressive neurological diseases. Finally, the experts were concerned about the generalizability of the observed results as they noted that a relatively low percentage of the population (10-15%) could be eligible for the medicinal product.

The patient representatives agreed with the above views. In the view of these patient representatives, the magnitude of the above-mentioned effect is not expected to significantly impact the life of patients.

[1] Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's Dement Transl Res Clin Interv 2019;5:354–63.;
El-Hayek YH, Wiley RE, Khoury CP, Daya RP, Ballard C, Evans AR, et al. Tip of the Iceberg: Assessing the Global Socioeconomic Costs of Alzheimer's Disease and Related Dementias and Strategic Implications for Stakeholders. J Alzheimers Dis 2019;70:321–39.

2. The SAG is asked to comment on the clinical relevance of ARIA-Es and ARIA-Hs and the manageability of these imaging abnormalities in clinical practice:

a. Does the SAG consider that the risk minimisation measures as proposed by the Applicant are sufficient to handle this risk?

The SAG-N experts overall considered that most proposed risk management measures may be difficult to implement in the real-world practice.

The contraindication in patients with MRI findings suggestive of severe cerebral amyloid angiopathy, defined as >4 microhaemorrhages or an area of superficial siderosis on pre-treatment magnetic resonance imaging (MRI) is feasible to implement.

It was considered that the discussion of the benefit - risk balance between the prescriber and the patient is difficult to be properly implemented as it must include the risk of not being eligible to receive antithrombotic medicinal products which implies to handle not only the risk inherited to Leqembi, but also the potential risk associated to not being eligible for these antithrombotic medicinal products. This includes acute thrombolytic treatment for stroke and ischemic heart disease. This was perceived by the SAG-N experts as a serious concern, even more so because the ApoE4 allele is also a risk factor for ischemic stroke. In case of a stroke leading to aphasia, the patient would not be capable to communicate that he/she is under Leqembi treatment in the emergency room (ER), but even without aphasia it may be difficult to accurately communicate medication treatment for patients with AD in the acute setting. It was considered that the patient card cannot completely overcome this situation as it is unlikely that the patient could always provide the card to the health care professional in ER who might not know about Leqembi and its potential risks. Overseeing the consequences of not being able to receive acute treatment for stroke, which is common in these older populations, when started on Leqembi, may be very challenging for patients and caregivers.

The SAG-N experts considered by consensus that the proposed MRI monitoring – at least 4 MRI within 14 months; more if there are findings- is a clear burden for the patients. The experts also agreed by consensus that the implementation of this MRI monitoring as proposed by the applicant may be unfeasible for many countries. An expert commented that it is unclear whether the MRI monitoring would be reliable enough using a 1.5 Tesla MRI. The necessity to use a 3.0 T MRI, would raise even more concerns on feasibility of MRI monitoring in clinical practice.

The patient representatives agreed that MRI monitoring is a clear burden for them. Further, it was noted that some patients need anxiolytic medicines to undergo MRI. Furthermore, they mentioned that it is frequently requested that caregiver goes with the patient which increases burden.

b. Does the SAG believe that there are subgroups of patients particularly harmed by the treatment (e.g. APOE4 carriers)? If APOE4 carriers are such population, should a mandatory testing for APOE4 be considered warranted before initiation of the treatment in order to properly mitigate the risk of ARIA (i.e. increase monitoring in this population)?

The SAG-N experts agreed by consensus that heterozygous and in particular homozygous ApoE carriers are a group of higher risk of adverse events. No further subgroups were identified.

The SAG-N experts agreed by consensus that ApoE4 genetic testing must be mandatory before treatment so the patients are fully informed, and the benefit and risks can be properly evaluated at individual level. In view of the high risk of ARIA, the SAG-N experts agreed by consensus that there should be a contraindication for homozygous ApoE4 carriers.

The SAG-N experts noted that genetic testing raises ethical concerns for the relatives and offspring and also for the patient as ApoE4 carries prognostic information (i.e. ApoE4 carriers harbour a worse prognosis but also a higher risk on ARIA under Leqembi treatment). Overall, experts considered that genetic testing is feasible, but that ethical concerns exist and are complex.

Patient representatives agreed with the above views. They concluded that genotyping should be mandatory because patients have the right to be fully informed on the associated risks in case of ApoE4 carriers.

3.7.3.2 Third parties

The CHMP received interventions from third parties. Overall, these third parties had expressing views about the epidemiology of Alzheimer disease, the unmet medical need, the scales for assessing efficacy of treatments, ARIA, and Outcomes in the clinical trials with lecanemab.

The CHMP expresses full agreement with the stated unmet need. Furthermore, the CHMP considered those interventions in the context of its assessment and concluded that the observations put forward were already known by CHMP, and as such had no impact on the CHMP conclusions.

3.8. Conclusions

The overall benefit/risk balance of Leqembi is negative.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Leqembi in the proposed indication in adult patients with mild cognitive impairment or mild dementia due to Alzheimer's disease (Early Alzheimer's disease) with confirmed amyloid pathology, and having considered all the available evidence including the responses submitted by the applicant in writing and during an oral explanation, as well as the outcome of the consultation with the Neurology scientific advisory group, and having considered the magnitude of benefits and risks, and the associated uncertainties, the CHMP considers by consensus that the safety of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

The magnitude of the effect of Leqembi does not outweigh the safety concerns:

- Lecanemab treatment causes amyloid-related imaging abnormalities (ARIA) in a significant proportion of treated patients. Clinical consequences may be serious in some patients and may include seizures and intracerebral haemorrhage;
- Notably, this risk is particularly pronounced in apolipoprotein E ε4 (ApoE ε4) homozygote carriers.

Therefore, it is the opinion of the CHMP that the benefit-risk balance of Leqembi is negative.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendices.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that lecanemab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Re-examination of the CHMP opinion of 25 July 2024

Following the CHMP conclusion that Leqembi was not approvable as its safety had not been sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation. The sections firstly report the whole content of the initial submission of the detailed grounds for re-examination. During the re-examination procedure the applicant has made additional submissions. These submissions clarified – in response to preliminary feedback during the re-examination procedure - that their target indication was changed to only include:

"Leqembi is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease**) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes** with confirmed amyloid pathology (see section 4.4)."

Accordingly, the focus of the assessment below will be the "restricted" population.

5.1.1. Written submission at the beginning of the re-examination procedure

5.1.1.1. Overall executive summary

Background on Alzheimer's Disease

Lecanemab was developed to slow the progression of Alzheimer's disease (AD) in patients who are at the earliest symptomatic stages. There is a pharmacological rationale to intervene whilst patients are at the earliest symptomatic stages (mild cognitive impairment [MCI] due to AD, mild AD). Progression of AD is measured by scales that assess key cognitive, functional and health-related quality of life items. There exist established scales to monitor the progression of AD and characterize the cognitive and functional abilities of patients. These include the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 item version (ADAS-Cog14) and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL) scales. Each scale measured items related to a patient's day to day activities such as memory, personal care, judgement and problem solving, and activities of daily living (ADL). The scales used in the pivotal study are established for use in AD because the disease itself is characterized by progressive cognitive decline and functional impairment that leads to an increasing loss of independence, and ultimately death.

The course of symptomatic disease occurs over approximately 10 years until death. Patients at the earliest symptomatic stages experience progressive cognitive decline and functional impairment through mild cognitive impairment; and at the mild AD dementia stage lose independence, requiring

assistance to perform usual daily functions (instrumental activities of daily living [ADL]) such as driving, cooking, shopping, and participating in social and community activities. By the moderate dementia stage of AD, the ability to perform these activities is completely lost and assistance is needed with basic activities of daily living (bathing, dressing, toileting), a complete lack of independence.

Systematic reviews and surveys demonstrate that patients with dementia, even in the earliest symptomatic stages, value their functional status, health-related quality of life, relationships, and independence, including their ability to continue working (if not retired). Understandably, the deterioration of these abilities at each successive stage of disease is distressing for patients and their families. There is clear importance to the patient to delay such progression.

ARIA With Lecanemab has Been Well Characterized in Study 301, With a Higher Incidence in Homozygous APOE4 Subjects

The key unfavourable effect of anti-amyloid treatments is symptomatic ARIA and ICH>1cm. ARIA occurs spontaneously in the absence of anti-amyloid therapies, however the rates are increased with anti-amyloid therapies like LEC10-BW, although the incidence and timing vary among treatments. These adverse events occur spontaneously in AD in the absence of anti-amyloid therapies due to underlying amyloid infiltration and resulting friability of cerebral blood vessels (cerebral amyloid angiopathy). ARIA-H is common in AD, irrespective of whether the patient receives anti amyloid therapy. Risk factors for ARIA-E, -H, and ICH>1 cm in natural history studies are cerebral amyloid angiopathy (CAA) (including evidence of prior microhaemorrhage and superficial siderosis) and an increasing number of *APOE4* alleles. *APOE4* is associated with increased cerebral amyloid deposition in blood vessel walls.

The incidence of these events in Study 301 Core are provided in Table 56.

Table 56. Comparison of safety outcomes at 18 months

Event at 18 months	**Overall Population – PBO**	**Overall Population – LEC10-BW**	**Noncarrier and Heterozygous *APOE4* Carrier Population – PBO**	**Noncarrier and Heterozygous *APOE4* Carrier Population – LEC10-BW**
ARIA-E	1.7%	12.6%	1.3%	8.9%
Overall ARIA-H	8.9%	16.9%	6.8%	12.9%
Isolated ARIA-H	7.7%	8.7%	5.9%	8.1%
ICH>1 cm[a]	0.2%	0.7%	0.3%	0.5%

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality- haemorrhage, ICH>1 cm = intracerebral haemorrhage greater than 1 cm in greatest diameter, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.
a: includes non-treatment emergent ICH>1 cm.

The timing of ARIA-E, -H, and ICH> 1 cm has been well characterized in Study 301. ARIA-E (and ARIA-H concurrent with ARIA-E) occurs early in treatment with the majority (~90%) occurring in the first 6 months, whereas isolated ARIA-H and ICH>1 cm occur across the treatment period. The proposed monitoring of patients outlined in the summary of product characteristics (SmPC), healthcare professional (HCP) guide and checklist reflect a magnetic resonance imaging (MRI) schedule covering the first 6 months of treatment.

ARIA-E and -H events are mostly asymptomatic. Symptomatic ARIA-E events were low (2.8% LEC10-BW Overall Population, 1.6% LEC10-BW Noncarrier and Heterozygous *APOE4* Carrier Population) and most ARIA-E events occurred early during treatment (~90%). When there are symptomatic events,

symptoms typically resolve. The incidence of serious symptomatic ARIA (-E, -H) events was low, and events tended to resolve without clinical or physiological sequelae; however, serious and life-threatening events secondary to ARIA-E and -H such as focal neurological findings and seizure rarely can occur (seizure as a symptom of ARIA; Overall Population: LEC10-BW 3/898 [0.0025 per patient-year of exposure], PBO 1/897 [0.0008 per patient-year of exposure] and Noncarrier and Heterozygous *APOE4* Population: LEC10-BW 1/757 [0.0010 per patient-year of exposure], PBO 1/764 [0.0010 per patient-year of exposure]).

In the Core, there was 1 death on PBO (0.0008 per patient-year of exposure) concurrent with ICH>1 cm and no deaths on LEC10-BW concurrent with ARIA-E, -H, or ICH>1 cm. In the Open-label Extension (OLE) Phase in Study 301 there were 3 deaths (0.0009 per patient-year of exposure) concurrent with ARIA-E, -H, or ICH>1 cm with LEC10-BW.

Notably, ARIA events are detectable, and the applicant has proposed a number of activities to (1) support HCPs in the monitoring for these events and, (2) to ensure HCPs are aware of appropriate patient management if these events occur. A Post Authorisation Safety Study (PASS) to further characterize ARIA-E, -H and ICH>1 cm, effectiveness of risk minimisation measures and drug utilisation is also proposed.

Collected postmarketing experience (up to 18 months) indicate that the rate of ARIA-E, -H, and ICH>1 cm reported is consistent with that observed in the clinical development programme. In the countries where lecanemab is approved, health systems, academic practices, and private practices have implemented workflows to ensure the application of the label instructions. This includes diagnosis with amyloid confirmation, baseline magnetic resonance imaging (MRI), and *APOE4* genotyping with consent for risk assessment, benefit-risk discussions, MRI monitoring, and ARIA management. These demonstrate the feasibility, alignment and effectiveness of labelling instructions and application of voluntary educational programs for ARIA.

In conclusion, the risks associated with LEC10-BW-treatment have been well characterized in the lecanemab development programme. Available postmarketing data is consistent with the safety profile observed in Study 301. The Applicant recognizes that in rare circumstances, there are symptomatic ARIA events with lecanemab which can be serious. It is important to note that whilst these rare symptomatic events do occur, the vast majority of ARIA are asymptomatic or resolve without symptoms or clinical sequalae and hence have minimal clinical impact on a patient's ability to continue LEC10-BW treatment. In practice, understanding of the risk of ARIA in the context of overall benefit will require careful discussion between patients and HCPs. In the pivotal study the majority of subjects experiencing ARIA events (90%) chose to continue LEC10-BW in the study which indicates that most patients and their HCP believed the potential benefits of continued treatment outweighed the potential risks. ARIA events are detectable, and the applicant has proposed a number of activities to support HCPs in the monitoring and appropriate patient management if these events occur.

Changes on Clinical Outcome Measures in Study 301 Show That Lecanemab Slows the Progression of Alzheimer's Disease and Maintains Patients' Independence for Longer

It is agreed by the CHMP that LEC10-BW demonstrated a treatment effect in Study 301.

In Study 301, LEC10-BW showed statistically significant slowing of clinical decline as measured by established, validated scales that assess key cognitive, functional and health-related quality of life outcomes. These scales measured items related to a patients' day to day activities such as memory, personal care, judgement and problem solving, and ADLs. The scales used in Study 301 are appropriate in AD because the disease itself is characterized by progressive cognitive decline and functional impairment that leads to an increasing loss of independence, and ultimately death.

Consistent results for the primary and key secondary outcomes were demonstrated for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population (Table 57).

Table 57. Comparison of efficacy outcomes at 18 months

Endpoint at 18 months	**Overall Population**	**Noncarrier and Heterozygous *APOE4* Carrier Population**
CDR-SB	27%	33%
ADAS-Cog14	26%	28%
ADCOMS	24%	28%
ADCS-MCI-ADL	37%	39%

ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14 item version, ADCOMS = Alzheimer's Disease Composite Score, ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, CDR-SB = Clinical Dementia Rating-Sum of Boxes.

Because of the pharmacological rationale to intervene early, patients with MCI due to AD or mild AD were defined as the population in which to initiate treatment; therefore, changes from baseline in the control group will be relatively small in absolute terms and the absolute magnitude of the difference between groups will be small, even if the effect in relative terms is relevant. Assessing the importance of slowing of disease progression at the group- or subject-level is therefore dependent on how the treatment effects are quantified and characterized. As an efficient approach to statistical analysis, one approach taken by the applicant was to consider the relevance of the mean difference between LEC10-BW and PBO on (pseudo) continuous outcome scales as primary and key secondary endpoints at 18 months. However, the applicant acknowledges that absolute mean treatment differences do not provide comprehensive characterisation of effects in terms of their importance to patients. As an alternative, and in line with 2002 EMA guidance, another way to characterize effects is to assess the proportion of patients preserved from meeting a milestone of deterioration over 18 or 36 months, or the reduction in risk of progression to next stage of disease (HR), whereby the next stages (mild AD [dependence on assistance to perform daily activities], moderate AD [no ability to perform daily activities]) reflect increasing loss of independence. These are milestones of clear clinical importance for patients.

Responder analyses evaluating the proportion of subjects worsening by meaningful amounts or thresholds of clear clinical importance are a standard approach to support assessment of the clinical relevance of treatment effect sizes. Responder analyses do this by incorporating a clinically relevant degree of disease progression at a subject-level.

These analyses showed that fewer subjects progressed to the next stage of disease with LEC10-BW, regardless of the threshold chosen. Time to progression to the next stage of AD was increased with LEC10-BW, with an estimated ~30% decrease in risk of progression at any given timepoint. Another approach taken by the applicant was to quantify in time the slowing of disease progression seen with treatment. Over an 18-month period, PBO subjects deteriorated approximately 6 months faster than with LEC10-BW. This represents "time saved" whereby LEC10-BW subjects are maintained in the earlier stages of disease.

In terms of expectations for treatment effects over the longer-term, LEC10-BW impacted biomarkers of amyloid, tau, and neurodegeneration, providing a biological basis for the treatment effects consistent with slowing of disease pathophysiology. Therefore, it is expected that the effects seen at 18 months will continue to expand over time as they did in the initial period of treatment and follow-up.

Data from the OLE Phase where LEC10-BW was assessed through 36 months show the slowing of disease progression at 18 months continues to accumulate over time. The mean treatment effect continues to increase over time, translating to further time preserved in earlier stages of disease. Similar to the time- saved analyses performed with actual 18 months data, projections performed by the applicant using actual 36 months data for LEC10-BW, PBO and a natural history cohort to assess the amount of time to convert to the next stage of AD estimate a difference in median time to progression of disease across the target population of 12 months and that over a 5-year period, the extent to which PBO subjects deteriorate would not be reached for LEC10-BW treated patients for another 18 months.

Consistent with the responder/progressor analyses, health-related quality of life outcomes reinforce that the changes seen on clinical scales after 18 months translate to tangible, meaningful benefits for patients and their care partners. Long-term data show that these benefits continue to increase over time. Unlike for PBO subjects, those treated with LEC10-BW had less decline in mood, self-care, finances and life as a whole. For care partners, for whom AD has an enormous detrimental impact, fewer felt as if their quality of life had suffered.

In conclusion, the convergence of evidence supports that the treatment effects seen at 18 months result in meaningful benefits for patients whereby they are able to maintain their independence for longer, and that that the meaningful benefits seen at 18 months continue to increase over time.

5.1.1.2. Background on Alzheimer's Disease

5.1.1.2.1. Alzheimer's Disease is a Relentless, Progressive Disease That Accelerates After the Early Alzheimer's Disease Stage

AD is an irreversible and progressive neurodegenerative disease that affects memory, thinking, and behaviour, and is ultimately fatal. While the clinical progression in early stages of AD is relatively linear, the overall trajectory through all stages of the disease is not, with the disease accelerating over time in the later stages (Figure 27). For this reason, earlier intervention before decline accelerates can slow the increasingly rapid accumulation of even more consequential, irreversible, functional losses and therefore provide increasing long-term benefits for patients.

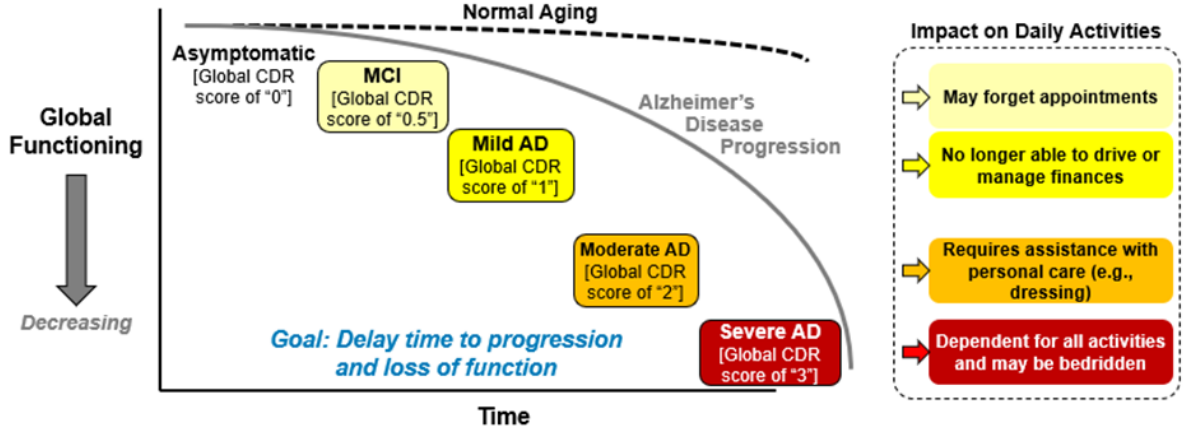


Figure 27. Depiction of AD decline across the continuum versus normal aging

AD = Alzheimer's disease, CDR = Clinical Dementia Rating, MCI = mild cognitive impairment.
Source: Sperling, et al., 2011 (adapted).

For patients, symptoms grow severe enough to interfere with daily tasks (feeding, dressing, bathing, continence) resulting in poor health-related quality of life and a loss of independence. The gradual progression of disease is distressing for patients, their care partners, and their families. The increased dependency and emotional changes contribute significantly to care partner burden, putting them at increased risk for physical morbidity and mental disorders (Sörensen and Conwell, 2011).

Early AD (MCI due to AD and mild AD dementia) is the stage of AD where compromised memory and thinking first appear, and may present as problems with memory, language, or judgement, as precursors to the beginning of functional decline associated with dementia. Early AD is often minimized and mistakenly attributed to normal aging. Early AD is not normal aging, as there is already cognitive impairment with amyloid plaques, neurofibrillary tangles, and resulting neuronal and synaptic dysfunction and loss in the brain. Patients with early AD cannot be characterized as "relatively healthy" from the perspective of brain health and daily functioning. In the earliest symptomatic stage of AD (MCI due to AD), a patient's cognitive function is impaired (Jekel, et al., 2015), with difficulties in coming up with words, losing items, and forgetting appointments and other important recent events. This can result in feelings of anxiety, shame and fear for the future; as well as the health and financial implications that arise from losing items, missing appointments, or impaired financial judgment. The ability to function and health-related quality of life will decline relentlessly to the point of severe dependence and then premature death (Tifratene, et al., 2015; Boyle, et al., 2006). By the mild AD stage, patients are impaired across daily activities and may no longer be able drive, work (if not retired), cook, or perform community activities without supervision, although basic activities such as bathing, dressing, and toileting are preserved. By the moderate AD stage, patients can no longer perform these instrumental daily activities, and basic activities become impaired.

In Europe, AD and other dementias were estimated to be the 3rd leading cause of death for people 70 years and older, with approximately 640,000 deaths attributable to dementia in this age group in 2017 (Ritchie, 2019).

5.1.1.2.2. Maintaining Patients in the Earliest Stages of Disease and Slowing the Disability Associated With Alzheimer's Disease is Clinically Meaningful

The concept of early treatment, delaying disability, and maintaining health-related quality of life is consistent with how HCPs approach AD and other serious progressive neurological conditions. The goal of early treatment is to slow overall progression and to modify the course of the disease, leading to longer periods of stability and functional independence.

Patients, care partners, and treating clinicians consistently highlight the importance of maintaining patients in the earlier stages of disease for longer where health-related quality of life and functional independence are maintained (Tochel, et al., 2019; DiBenedetti, et al., 2020). Systematic reviews and surveys demonstrate that patients with dementia, even in the earliest stages, value their functional status, health-related quality of life, relationships, and independence, including their ability to continue working (if not retired) (Wehrmann, et al., 2021, Watson, et al., 2019 and Tahami-Monfared, et al., 2022). These deteriorate with each successive stage of disease.

When quantified to actual daily benefit to the patient with early AD, and from the standpoint of the care partner and the treating clinician, there are several urgent treatment needs, which lecanemab is intended to help address:

1. Maintaining independence by maintaining the core abilities of cognition, daily function, and behaviour; each of which become severely impaired over the course of the disease.
2. Slowing the disability associated with AD such that individuals remain at milder, less debilitating, and less costly stages.

3. Maintaining health-related quality of life for both the patient and care partners, given that AD has an enormous detrimental impact on care partners and often multiple family members, in addition to its impact on patients themselves.

5.1.1.3. ARIA With Lecanemab has Been Well Characterised in Study 301, with a Higher Incidence in Homozygous APOE4 Subjects

5.1.1.3.1. Safety Executive Summary

ARIA is characterized as either ARIA with oedema (ARIA-E), which can be observed on MRI as brain oedema or sulcal effusions, or ARIA with hemosiderin deposition (ARIA-H), which includes cerebral microhaemorrhage and superficial siderosis. ARIA is an MRI radiographic finding that can occur spontaneously in AD in the absence of anti-amyloid therapies and is usually asymptomatic.

ICH>1 cm in diameter will be discussed in this section, although this event is not considered a type of ARIA. ICH>1 cm in the lobar brain regions can occur spontaneously in AD in the absence of anti-amyloid therapies and can cause focal neurological symptoms (ICH>1 cm in the deep brain regions or brain stem is usually related to hypertension).

ARIA-E, -H, and ICH>1 cm occur spontaneously in AD in the absence of anti-amyloid therapies due to underlying amyloid infiltration and resulting friability of cerebral blood vessels (CAA). ARIA-H is typically concurrent with ARIA-E and there is a high background rate in AD, irrespective of whether the patient receives anti-amyloid therapy. In epidemiologic and AD clinical studies, the background rates of ARIA are:

- ARIA-E rate in PBO arms of clinical trials ranges from 1.7% – 2.7% over 18 months (Honig, et al., 2024)
- ARIA-H rate in PBO arms of clinical trials ranges from 8.6% – 13.6% over 18 months (Honig, et al., 2024).
- ICH>1 cm rate in PBO arms of AD clinical trials ranges from 0.4% – 1% (Honig, et al., 2024); and a meta-analysis of observational studies found rates of ICH>1 cm in AD of 2.7 – 5.2 per 1000 person-years (Waziry, et al., 2020).

Risk factors for ARIA-E, -H, and ICH>1 cm in natural history studies (without anti-amyloid therapies), PBO, or anti-amyloid therapies, are CAA (including evidence of prior microhaemorrhage and superficial siderosis) and an increasing number of *APOE4* alleles (Ulrich, et al., 2018; Piazza, et al., 2022). *APOE4* is associated with increased cerebral amyloid deposition in blood vessel walls (Antolini, et al., 2021).

Additional risk factors for ICH>1 cm include the use of anticoagulants and thrombolytics.

With anti-amyloid therapies, the risk of developing ARIA-E (and ARIA-H concurrent with ARIA-E) is highest when first starting the anti-amyloid therapy (Filippi, et al., 2022; Wang, et al., 2022), whereas isolated ARIA-H and ICH>1 cm are distributed throughout the treatment period for both PBO and anti-amyloid therapies, including lecanemab.

- In Study 301 Core:
  - The incidence of ARIA-E with LEC10-BW in the Overall Population was 12.6% (vs 1.7% PBO). Of the genotypes, homozygous *APOE4* carriers had a higher incidence (32.6%). When homozygous *APOE4* carriers are removed from the analyses (Noncarrier and Heterozygous *APOE4* Carrier Population) the incidence was 8.9% (vs 1.3% PBO).
  - The incidence of overall ARIA-H with LEC10-BW in the Overall Population was 16.9% (vs 8.9% PBO). Of the genotypes, homozygous *APOE4* carriers had a higher incidence (38.3%). For the

Noncarrier and Heterozygous *APOE4* Carrier Population the incidence was 12.9% (vs 6.8% PBO).

- The incidence of isolated ARIA-H (occurring in the absence of ARIA-E) with LEC10-BW in the Overall Population was 8.7% (vs 7.7% PBO). The excess incidence of ARIA-H (overall ARIA-H) with LEC10-BW is related to ARIA-H that is concurrent with ARIA-E.
- The incidence of ICH>1 cm with LEC10-BW was low, 6/898 (0.7%) (vs 2/897 [0.2%] PBO) in the Overall Population (note: the values for ICH>1 cm reflect all reported cases, not only those defined as treatment-emergent). Although there were few events reported which limits the ability to draw conclusions, of the genotypes, homozygous *APOE4* carriers had a higher incidence of ICH>1 cm (2/141 [1.4%]). For the Noncarrier and Heterozygous *APOE4* Carrier Population the incidence was 4/757 (0.5%) (vs 2/764 [0.3%] PBO).

- The timing of ARIA-E, -H, and ICH> 1 cm has been well characterized. ARIA-E (and ARIA-H concurrent with ARIA-E) occurs early in treatment with the majority (~90%) occurring in the first 6 months, whereas isolated ARIA-H and ICH>1 cm occur across the treatment period. ARIA-E and -H events are mostly asymptomatic, and when there are symptomatic events, the symptoms typically resolve.

- There were few subjects (2.2% Overall Population) who discontinued LEC10-BW due to ARIA (-E, -H) during the Core. The majority of subjects with ARIA (~90%) continued in the study (i.e., most patients and Principal Investigators elected to continue treatment).

- The incidence of serious symptomatic ARIA-E and -H events was low, and events tended to resolve without sequelae; however, serious and life-threatening events secondary to ARIA-E and –H, such as focal neurological findings and seizure, rarely can occur (seizure as a symptom of ARIA; Overall Population: LEC10-BW 3/898 [0.0025 per patient year of exposure], PBO 1/897 [0.0008 per patient-year of exposure] and Noncarrier and Heterozygous *APOE4* Population: LEC10-BW 1/757 [0.0010 per patient-year of exposure], PBO 1/764 [0.0010 per patient-year of exposure]).

- In the Core there were no deaths on LEC10-BW and 1 death (0.0008 per patient-year of exposure) with concurrent ICH>1 cm in PBO: 1 (noncarrier) subject. In the OLE Phase, there were 3 deaths (0.0009 per patient-year of exposure) with concurrent ARIA-E, -H, or ICH>1 cm: 1 (homozygous *APOE4* carrier) subject with multiple ICH>1 cm after tissue plasminogen activator (tPA); 1 (noncarrier) subject with subacute ICH>1 cm; and 1 (homozygous *APOE4* carrier) subject with severe ARIA-E and concurrent ARIA-H microhaemorrhage. Overall, deaths, and deaths with concurrent ARIA, when adjusted to patient-years of exposure, are similar for LEC10-BW and PBO.

- The incidence of symptomatic ARIA-E with LEC10-BW was low (2.8% Overall Population and 1.6% Noncarrier and Heterozygous *APOE4* Population), when ARIA-E symptoms did occur, all resolved during the period of observation except 1 patient had residual headache (this subject did not enter the OLE Phase and there was no opportunity to determine if the headache resolved). Of the patients who had symptomatic ARIA-H in the Overall Population, a total of 5/898 (0.6%) LEC10-BW subjects had residual symptoms (headache, dizziness, malaise, gait disturbance, retinal haemorrhage) and 1/897 (0.1%) PBO subject had residual symptoms (migraine).

- Extensive analyses demonstrate that events of ARIA-E and -H are not associated with accelerated long-term progression and that resumption of treatment after dosing pauses is not associated with increased ARIA-E or -H recurrence.

- Collected postmarketing experience (up to 18 months) indicate that the rate of ARIA-E, H, and ICH>1 cm reported is consistent with that observed in the clinical development programme. In the

countries where lecanemab is approved, health systems, academic practices, and private practices have implemented workflows to ensure the application of the label instructions. This includes diagnosis with amyloid confirmation, baseline MRI, and *APOE4* genotyping with consent for risk assessment, benefit-risk discussions, MRI monitoring, and ARIA management. These demonstrate the feasibility, alignment and effectiveness of labelling instructions and application of voluntary educational programs for ARIA.

- In rare circumstances, there are symptomatic ARIA events with LEC10-BW, which can be serious and do not resolve. It is important to note that whilst these rare symptomatic events do occur, the vast majority of ARIA are asymptomatic or resolve without symptoms or clinical sequalae and hence have minimal clinical impact on a patient's ability to continue LEC10-BW treatment. Notably, ARIA events are detectable, and the applicant proposed a number of activities to support HCPs in the monitoring for these events and to ensure HCPs are aware of appropriate patient management if these events occur:
    - In addition to excluding homozygous *APOE4* carriers from the proposed indicated population, the proposed SmPC contraindicates treatment in subjects with pretreatment MRI findings suggestive of severe CAA (defined as >4 microhaemorrhages or an area of superficial siderosis). The SmPC also states that treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of AD, in centres with timely access to MRI. A baseline MRI (within 6 months) prior to initiating treatment to evaluate for pre-existing ARIA is required. The SmPC provides detailed guidance on MRI monitoring, including the need for enhanced clinical vigilance during the first 14 weeks of treatment, and if a patient experiences symptoms suggestive of ARIA. Dosing instructions based on radiographic and clinical symptoms (including reference to focal neurologic deficits that can mimic ischemic stroke for ARIA-E) are outlined. Physicians are instructed to permanently discontinue treatment in certain scenarios of ARIA-E, -H, and ICH>1 cm.
    - An HCP Guide and Checklist, and Patient Alert Card were proposed for use prior to administration of lecanemab, and educational materials covering ARIA-E, -H, and ICH>1 cm will also be available for HCPs.
    - Pharmacovigilance activities including a follow up questionnaire to be used by HCPs when reporting postmarketing ARIA-E, -H, and ICH>1 cm events is proposed to support the characterisation of these events, with this data to be reported in Periodic Safety Update Reports (PSURs).
    - A PASS (an all-EU patients study) to further characterize ARIA-E, -H and ICH>1 cm, effectiveness of RMMs and drug utilisation is proposed.

In conclusion, the risks associated with LEC10-BW-treatment have been well characterized in the lecanemab development programme. Available postmarketing data is consistent with the safety profile observed in Study 301. Whilst the vast majority of ARIA events are asymptomatic and without clinical or physiological sequalae, the applicant recognizes that that symptomatic ARIA events do not always resolve and can be serious and life-threatening. ARIA events are detectable, and the applicant has proposed a number of activities to support HCPs in the monitoring and appropriate patient management if these events occur. In the countries where lecanemab is approved, health systems, academic practices, and private practices are implementing workflows to ensure the application of the label instructions.

There is significant morbidity and mortality associated with AD (Lanctôt, et al., 2024). As illustrated in the clinical studies with lecanemab, patients who were well informed on the risks (without knowing

treatment assignment) made an informed decision to participate given the significant impact AD has on their lives, and the lives of their care partners and families.

5.1.1.3.2. Real-World Experience with Lecanemab

Within this document the following postmarketing information is presented for ARIA-E, ARIA-H, seizure, and ICH>1 cm: overall, serious events, symptomatic events, and fatal events. The data is based on a search of the Eisai Lecanemab Global Safety Database for serious and nonserious spontaneous and solicited reports of events coded to specific MedDRA preferred terms that were received or had an event onset date from the International Birth Date (IBD) (06 Jan 2023) through 05 Jul 2024.

The majority of spontaneous and noninterventional solicited reports are from the US. To date, the estimated exposure is more than 3125 patient-years (based on over 180,000 vials distributed) in the US (with a small number from China). This estimated exposure does not include the Japanese postmarketing setting.

Considering that the specific number of patients treated commercially with lecanemab is not known, the incidence of ARIA and ICH from spontaneous and solicited reporting cannot be calculated. Therefore, this estimated exposure is what is used as the denominator for the reporting rates below. However, given that ARIA-E are expected to occur early in the course of treatment (i.e., within the first 4-6 months), the use of this denominator for reporting rates is likely to overstate what the incidence would be if calculated based on patients exposed. For example, if 7,000 patients were exposed for 4 months, then the reporting rate for fatal ARIA-E would be 0.04% whereas based on patient-years it is approximately 0.1%. It is also important to note that serious and fatal events are more likely to be reported than non-serious events and also that for medications such lecanemab that have received substantial media attention reporting rates are likely to be higher than for other medications.

Postmarketing data was collected in Japan as part of the study BAN2401-J081-401.

As of 05 Jul 2024, there were approximately 2440 patients treated with lecanemab who have been enrolled in the study.

A search was performed in the Japanese postmarketing safety database for serious and nonserious events using the same search strategy as used for the spontaneous and noninterventional solicited reports that were received or had an event onset date from the start of the study through 05 Jul 2024.

Presentations and Publications

The following presentations and publications providing information on physician experience with lecanemab are included in this submission:

- Clinical Experience With Amyloid Lowering Treatments in an Academic Dementia Specialty Practice (Washington University Experience presented at the Alzheimer's Association International Conference [AAIC] 2024): Implementing anti amyloid immunotherapy in the clinic is possible. The rate of ARIA was ~19.5%, which was expected based on clinical trials. Most ARIA is mild and asymptomatic. Occasional patients (2/154, 1.3%) develop clinically severe ARIA. The rate of infusion reactions was ~38.7%, which was higher than expected. The most common infusion reactions were headache, fever, and chills (Paczynski, et al, 2024).

- Clinical Use of Lecanemab at an Academic Medical Center (Columbia University Experience presented at AAIC 2024): Overall, with up to 21 infusions per patient, findings at the centre suggest that experience in clinical use may not be dissimilar to that in the clinical trials (Honig, et al., 2024A).

- Specialized Infrastructure in a Tertiary Hospital to Administer Disease Modifying Treatments in Alzheimer's Disease (Israel experience presented at AAIC 2024): Health systems have implemented workflows to ensure the application of the label instructions (Nathan, et al., 2024).
- Komodo US Database Experience (abstract submitted to the Clinical Trials on Alzheimer's Disease [CTAD] 2024): Lecanemab appeared to be utilized in appropriate patient populations within the dosing and monitoring guidelines in the Food and Drug Administration (FDA) approved label (Sabbagh, et al., 2024).

5.1.1.3.3. ARIA-E

ARIA-E occurs spontaneously in AD in the absence of anti-amyloid therapies due to underlying amyloid infiltration and resulting friability of cerebral blood vessels (CAA). In AD clinical trials, the rate of ARIA-E in PBO subjects ranges from 1.7% – 2.7% over 18 months (Honig, et al., 2024).

ARIA-E is characterized as the extravasation of fluid resulting in interstitial vasogenic oedema or sulcal effusion in the leptomeningeal/subpial space (Hampel, et al., 2022). The radiographic severity of ARIA-E is dependent on the location and extent of the finding. The sulcal effusion/exudates in ARIA-E may reflect leakage of proteinaceous fluid that is limited to the leptomeningeal/subpial space (Sperling, et al., 2011; Barakos, et al., 2013). Both forms of ARIA-E are typically transient and are not associated with restricted MRI diffusion, thus differentiating it from ischemia.

Risk factors for ARIA-E are CAA and cerebral microhaemorrhages (Ulrich, et al., 2018; Piazza, et al., 2022). Increasing number of *APOE4* alleles is also a risk factor for ARIA-E, as the presence of alleles is associated with increased cerebral amyloid deposition in blood vessel walls (Antolini, et al., 2021). Subjects with *APOE4* alleles have higher risks of CAA and cerebral microhaemorrhages (Ulrich, et al., 2018; Piazza, et al., 2022), irrespective of whether they receive anti-amyloid therapies. With anti-amyloid therapies, the risk of developing ARIA-E is highest when first starting treatment (Filippi, et al., 2022; Wang, et al., 2022).

In Study 301 Core, for the Overall Population the incidence of ARIA-E was lower in PBO (15/897 [1.7%]) (0.0121 per patient-year of exposure) than LEC10-BW (113/898 [12.6%]) (0.0959 per patient-year of exposure). Of the genotypes, homozygous *APOE4* carriers had a higher incidence of ARIA-E (5/133 [3.8%] PBO, 46/141 [32.6%] LEC10-BW). When homozygous *APOE4* carriers are removed from the analyses (Noncarrier and Heterozygous *APOE4* Carrier Population), the incidence was 10/764 (1.3%) subjects on PBO (0.0048 per patient-year of exposure) and 67/757 (8.9%) subjects on LEC10-BW (0.0461 per patient-year of exposure).

In the OLE Phase ("LEC10-BW Treated Period" which represents all subjects treated with LEC10-BW in the Core and OLE Phase), in the Noncarrier and Heterozygous *APOE4* Carrier Population the incidence was 146/1366 (10.7%) (0.0491 per patient-year of exposure).

Across both the Core and OLE Phase, ARIA-E occurred early in treatment irrespective of genotype, with the majority (~90%) occurring in the first 6 months. Most ARIA-E resolved both radiographically and clinically by 4 months.

In the Core, the incidence of symptomatic ARIA-E in the Noncarrier and Heterozygous *APOE4* Carrier Population was low with LEC10-BW, 12/757 (1.6%), and events were mostly mild or moderate in severity. The most common symptoms were headache, confusional state, dizziness, and nausea; however, serious and life-threatening symptoms, including seizure and status epilepticus, rarely can occur (seizure as a symptom of ARIA; Overall Population: LEC10-BW 3/898 [0.0025 per patient-year of exposure], PBO 1/897 [0.0008 per patient-year of exposure] and Noncarrier and Heterozygous

APOE4 Population: LEC10-BW 1/757 [0.0010 per patient-year of exposure], PBO 1/764 [0.0010 per patient-year exposure]).

In response to CHMP questions, the applicant evaluated concomitant anticoagulant and/or antiplatelet use and the risk of ARIA-E. The use of antiplatelets and anticoagulants demonstrated no increased incidence of ARIA-E when used with LEC10-BW versus LEC10-BW alone.

In the Core, there were no deaths on LEC10-BW and 1 death (0.0008 per patient-year of exposure) with concurrent ICH>1 cm in PBO: 1 (noncarrier) subject. In the OLE Phase, there were 3 deaths (0.0009 per patient-year of exposure) with concurrent ARIA-E, -H, or ICH> 1 cm: 1 (homozygous *APOE4* carrier) subject with multiple ICH>1 cm after tissue plasminogen activator (tPA); 1 (noncarrier) subject with subacute ICH>1 cm; and 1 (homozygous APOE4 carrier) subject with severe ARIA-E and concurrent ARIA-H microhaemorrhage. Overall, deaths, and deaths with concurrent ARIA, when adjusted to patient-years of exposure, are similar for LEC10-BW and PBO.

Notably, ARIA events are detectable, and the applicant has proposed a number of activities to (1) support HCPs in the monitoring for these events and, (2) to ensure HCPs are aware of appropriate patient management if these events occur. The proposed SmPC indication excludes homozygous *APOE4* carriers and provides details for physicians regarding the detection and clinical management of patients who experience ARIA-E events. Pharmacovigilance activities including a follow up questionnaire to be used by HCPs when reporting postmarketing ARIA-E events as well as a PASS to further characterize ARIA-E, -H and ICH>1 cm, effectiveness of RMMs, and drug utilisation is also proposed.

Collected postmarketing experience (up to 18 months) indicates that the rate of ARIA-E reported is consistent with that observed clinical development programme.

The Applicant recognizes that in rare circumstances, there are symptomatic ARIA events with LEC10-BW, which can be serious and do not resolve. It is important to balance these rare events against the majority of ARIA events, which resolve without symptoms or clinical or physiological sequalae. It is important to note that whilst these rare symptomatic events do occur, the vast majority of ARIA are asymptomatic or resolve without symptoms or clinical sequalae and hence have minimal clinical impact on patient's ability to continue LEC10-BW treatment.

The ARIA-E summary that follows contains both previously submitted and new analyses, with new analyses or content identified.

The long-term consequences of ARIA-E is discussed in 5.1.1.3.9. .

(1) Incidence and Radiographic Severity of ARIA-E

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

In Study 301 Core, the incidence of treatment-emergent ARIA-E was lower in PBO than LEC10-BW (Table 58). Of the genotypes, homozygous *APOE4* carriers had a higher incidence of ARIA-E (46/141 [32.6%]) compared to noncarriers (15/278 [5.4%]) and heterozygous *APOE4* carriers (52/479 [10.9%]).

Table 58. Incidence of treatment-emergent ARIA-E – study 301 core (safety analysis set)

Population	Placebo n/m (%)	Lecanemab 10 mg/kg Biweekly n/m (%)
Overall	15/897 (1.7)	113/898 (12.6)
Noncarrier and Heterozygous *APOE4* Carrier	10/764 (1.3)	67/757 (8.9)
Individual Genotype		
Noncarriers	1/286 (0.3)	15/278 (5.4)
Heterozygous *APOE4*	9/478 (1.9)	52/479 (10.9)
Homozygous *APOE4*	5/133 (3.8)	46/141 (32.6)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, m = number of subjects in each category, n = number of subjects with an event in each category.
Source: Appendix 1 Table 14.3.2.6.10 and Study 301 Core CSR Table 14.3.2.6.10.

Figure 28 shows that treatment-emergent ARIA-E events in PBO were distributed over the course of treatment; however. most cases of ARIA-E (~90%) with LEC10-BW occurred within the first 6 months of treatment. *APOE4* genotype had no impact on the timing of ARIA-E.

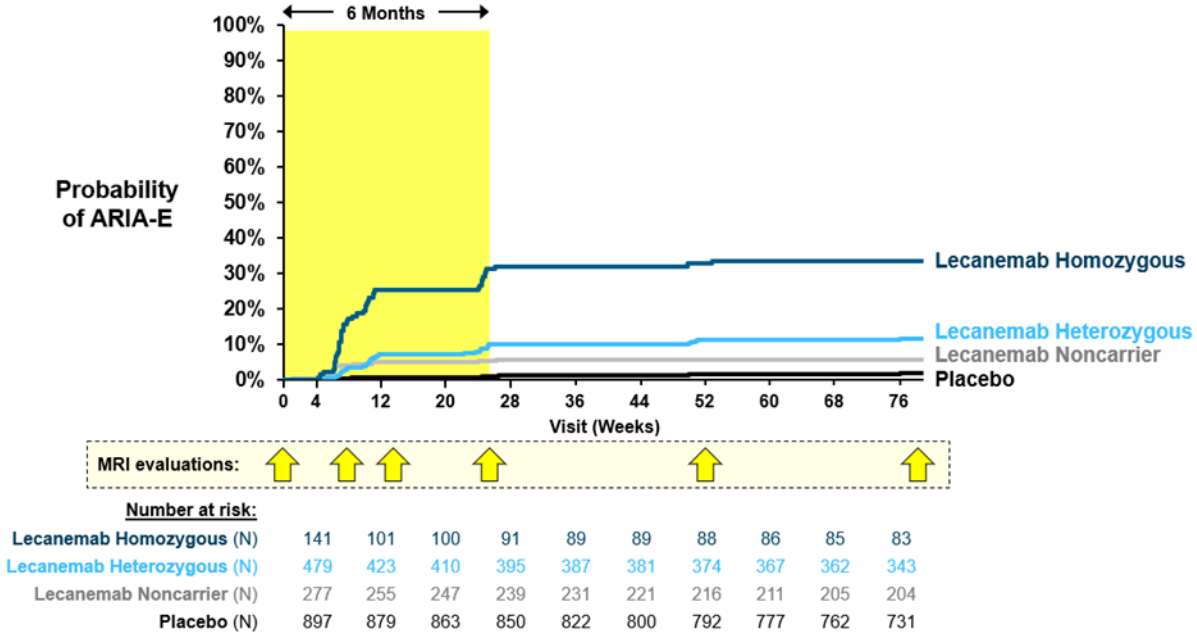


Figure 28. Kaplan-Meier curves for time to first ARIA-E for the overall population – study 301 core (safety analysis set)

ARIA-E = amyloid-related imaging abnormality-oedema/effusion, MRI = magnetic resonance imaging.
Source: Study 301 Core CSR Figure 14.3.2.6.1.

The majority of treatment-emergent ARIA-E were mild to moderate radiographically (Table 59). There was a shift toward greater radiographic severity in homozygous *APOE4* carriers relative to other genotypes. Most ARIA-E resolved radiographically by 4 months, with ~30% resolving within 60 days, ~50% resolving within 90 days, ~80% resolving within 120 days, and all resolved by the end of the Core. Across *APOE4* genotypes, timing and rate of ARIA-E resolution were similar with most resolving within 4 months (Study 301 Core Clinical Study Report [CSR] Table 14.3.2.6.18).

Table 59. Radiographic severity of treatment-emergent ARIA-E – study 301 core (safety analysis set)

	Placebo n/m (%)			**Lecanemab 10 mg/kg Biweekly n/m (%)**		
	Radiographic Severity			**Radiographic Severity**		
Population	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Overall	9/897 (1.0)	6/897 (0.7)	0	37/898 (4.1)	66/898 (7.3)	9/898 (1.0)
Noncarrier and Heterozygous *APOE4* Carriers	7/764 (0.9)	3/764 (0.4)	0	31/757 (4.1)	33/757 (4.4)	2/757 (0.3)
Individual Genotype						
Noncarriers[a]	0	1/286 (0.3)	0	6/278 (2.2)	9/278 (3.2)	0
Heterozygous *APOE4* Carriers[b]	7/478 (1.5)	2/478 (0.4)	0	25/479 (5.2)	24/479 (5.0)	2/479 (0.4)
Homozygous *APOE4* Carriers[c]	2/133 (1.5)	3/133 (2.3)	0	6/141 (4.3)	33/141 (23.4)	7/141 (5.0)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, m = number of subjects in each category, n = number of subjects with an event in each category.
a: Among all noncarriers in the lecanemab group with radiographic ARIA-E (n=15), the distribution was 6/15 (40.0%) mild and 9/15 (60.0%) moderate.
b: Among all heterozygous *APOE4* carriers in the lecanemab group with radiographic ARIA-E (n=52), the distribution was 25/52 (48.0%) mild, 24/52 (46.2%) moderate, and 2/52 (3.8%) severe.
c: Among all homozygous *APOE4* carriers in the lecanemab group with radiographic ARIA-E (n=46), the distribution was 6/46 (13.0%) mild, 33/46 (71.7%) moderate, and 7/46 (15.2%) severe.
Source: Appendix 1 Table 14.3.2.6.10.2 and Study 301 Core CSR Table 14.3.2.6.10.2.

Study 301 Open Label Extension (36 Months Total Treatment)

Data presented for Study 301 OLE Phase are cumulative for any subject who received at least 1 dose of LEC10-BW at any time, whether in the Core Study or OLE Phase (data cutoff 31 Mar 2024) (i.e., LEC10-BW Treated Period). Therefore, these data are a pooled presentation of all LEC10-BW treated subjects across the total duration of Study 301. Data presented for the OLE Phase reflect up to 36 months treatment with LEC10-BW.

The incidence of treatment-emergent ARIA-E in the LEC10-BW Treated Period (Table 60) remained consistent with the Core, with the slight increase in ARIA-E (Overall Population: 12.6% Core, 14.7% LEC10-BW Treated Period; Noncarrier and Heterozygous *APOE4* Carrier Population: 8.9% Core, 10.7% LEC10-BW Treated Period) due to Core PBO-treated subjects receiving LEC10-BW for the first time in the OLE Phase. The incidence of ARIA-E with longer-term treatment was similar to the Core when assessed by genotype.

Table 60. Incidence of treatment-emergent ARIA-E – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	**LEC10-BW n/m (%)**
Overall	238/1616 (14.7)
Noncarrier and Heterozygous *APOE4* Carriers	146/1366 (10.7)
Individual Genotype	
Noncarriers	34/497 (6.8)
Heterozygous *APOE4* Carriers	112/869 (12.9)
Homozygous *APOE4* Carriers	92/250 (36.8)

LEC10-BW-Treated Period includes Core Study and OLE Phase in which subjects received LEC10-BW. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received LEC10-BW from the OLE Phase, and is the Core Study baseline for subjects who received LEC10-BW from the Core Study. A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. If a subject had two or more ARIAs with different severities, then the event with the maximum severity was used for that subject. Data collected after subjects switch to/start subcutaneous dose are not included.
AE = adverse event, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, *APOE4* = apolipoprotein E4 variant, ARIAs = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category, n = number of subjects with an event in each category. OLE = open-label extension, TEAE = treatment-emergent adverse event.
Source: Appendix 1 sCSR5 Table 14.3.2.6.1a.

A longer period of follow-up in the OLE Phase (up to 36 months) continues to show that most cases of ARIA-E (~90%) with LEC10-BW occur within the first 6 months of treatment (Figure 29). While *APOE4* genotype has an impact on the incidence, it has no impact on the timing of ARIA-E.

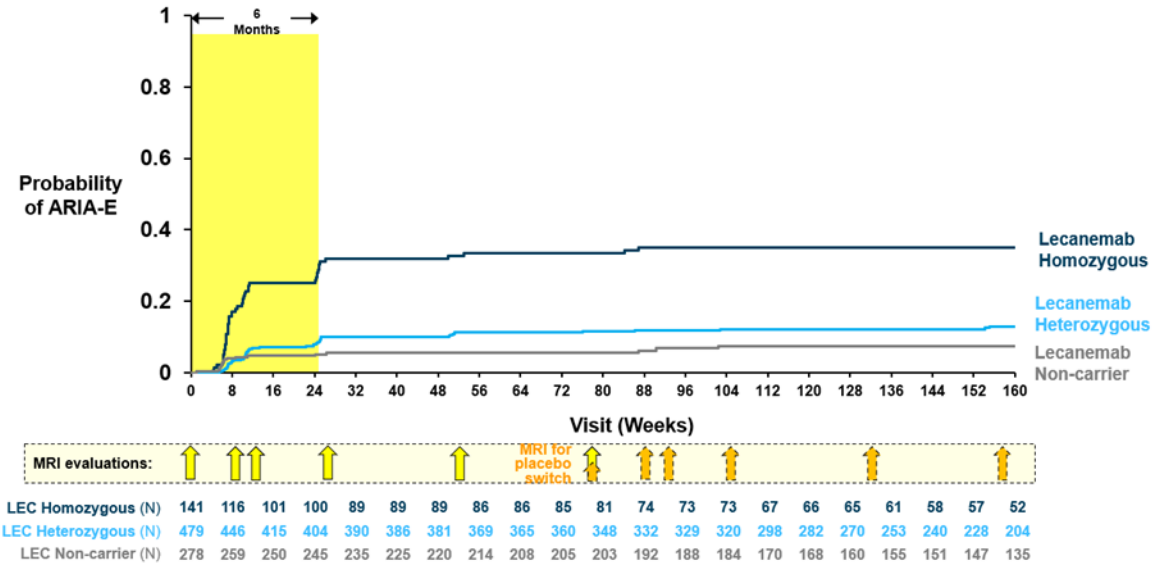


Figure 29. Kaplan-Meier curves for time to first ARIA-E for the overall population in core lecanemab group by APOE4 genotype – study 301 core and OLE phase (safety analysis set)

ARIA-E = amyloid-related imaging abnormality-oedema/effusion. Time to first ARIA-E is defined as time from first dose to onset of first ARIA-E. Time to first ARIA-E will be censored at the earliest of the last IV dose date + 30 days. Data collected after subjects switch to/start subcutaneous dose are not included.

Source: Appendix 1 sCSR5 Figure 14.3.2.6.3.

Consistent with the Core, the majority of ARIA-E was mild to moderate radiographically (Table 61). There was a shift toward greater radiographic severity in homozygous *APOE4* carriers relative to other genotypes.

Table 61. Treatment-emergent ARIA-E by maximum radiographic severity and APOE4 genotype – study 301 OLE – LEC10-BW-treated period (safety analysis set)

	Lecanemab 10 mg/kg Biweekly				
	Maximum Radiographic Severity n/m (%)				
Population (n, %)	**Questionable**	**Mild**	**Moderate**	**Severe**	**Missing**
Overall (238/1616 [14.7%]) [a]	1/1616 (0.1)	70/1616 (4.3)	139/1616 (8.6)	27/1616 (1.7)	1/1616 (0.1)
Noncarrier and Heterozygous *APOE4* Carriers (146/1366 [10.7%]) [a]	1/1366 (0.1)	53/1366 (3.9)	78/1366 (5.7)	13/1366 (1.0)	1/1366 (0.1)
Individual Genotype					
Noncarriers (34/497 [6.8%])[a]	0	14/497 (2.8)	20/497 (4.0)	0	0
Heterozygous *APOE4* Carriers (112/869 [12.9%])[a]	1 (0.1)	39/869 (4.5)	58/869 (6.7)	13/869 (1.5)	1/869 (0.1)
Homozygous *APOE4* Carriers (92/250 [36.8%])[a]	0	17/250 (6.8)	61/250 (24.4)	14/250 (5.6)	0

a. Subjects with any ARIA-E
LEC10-BW-Treated Period includes Core Study and OLE Phase in which subjects received LEC10-BW. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received LEC10-BW from the OLE Phase, and is the Core Study baseline for subjects who received LEC10-BW from the Core Study. A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.
If a subject had 2 or more ARIAs with different severities, then the event with the maximum severity was used for that subject. Data collected after subjects switch to/start subcutaneous dose are not included.
AE = adverse event, ARIA-E = amyloid related imaging abnormality oedema/effusion, *APOE4* = apolipoprotein E4 variant, ARIAs = amyloid related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, OLE = open-label extension, TEAE = treatment-emergent adverse event.
Source: Appendix 1 sCSR5 Table 14.3.2.6.10.2a.

Postmarketing Experience (up to 18 Months Experience)

Pharmacovigilance (PV) summary contained in this section is new for the re-examination procedure.

The following PTs were used for ARIA-E: amyloid related imaging abnormalities – oedema/effusion, vasogenic cerebral oedema and brain oedema. Additionally, a search for the PT of amyloid related imaging abnormalities has been included in this section.

There have been 101 events of ARIA-E and 33 reports of ARIA without further description provided regarding the type of ARIA.

While the relative proportion among all ARIA reports of serious and symptomatic spontaneous and solicited reports was higher than that observed in Study 301, it would be expected that serious and symptomatic cases are more likely to be reported spontaneously than asymptomatic cases. Additionally, the solicited reports are largely from patient support programs run by specialty pharmacies, which are more likely to receive information about lecanemab interruptions and are therefore more likely to be more severe events.

The majority of reports of ARIA-E were non-serious (75%), asymptomatic (62%) and occurred early in treatment with all occurring prior to the 14th dose of lecanemab.

When the radiographic severity was known, the majority of reports were mild to moderate in severity (28/32 [87%]). When *APOE4* genotype was known, 18% (8/45) of ARIA-E occurred in noncarriers, 47% (21/45) in heterozygous *APOE4* carriers, and 36% (16/45) in homozygous *APOE4* carriers; additionally, there was 1 report in an *APOE4* carrier where the genotype was not known.

Additionally, there were 33 reports of ARIA without further description provided regarding the type of ARIA despite attempts to obtain follow up. These reports generally had limited information, but most were nonserious (75%) and asymptomatic (69%).

Acknowledging the limitations of spontaneous reporting, and that the specific number of patients treated commercially with lecanemab is not known, and a reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, the rate (based on an estimated reporting rate of 0.03 events/patient-year of exposure) and severity of ARIA-E is consistent with that observed in the clinical development programme.

A summary of reports of ARIA-E has been provided by the applicant in the re-examination documentation.

Postmarketing safety data from approximately 2440 patients treated with lecanemab is available from Japan.

The incidence of ARIA-E was 1.1%. *APOE4* genotype data is limited due to access to *APOE4* testing in Japan. The majority of reports of ARIA-E were nonserious (82%), asymptomatic (82%), and occurred early in treatment with all occurring prior to the 6th dose of lecanemab. When the radiographic severity was known, the majority of reports were mild to moderate in severity (87%).

Additionally, there were 2 reports of ARIA, both nonserious and asymptomatic, without further information regarding the type of ARIA. The latency to onset and radiographic severity in both reports was not known.

(2) Serious Adverse Events due to ARIA-E

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

In the Overall Population there were no events of treatment-emergent serious ARIA-E in PBO, and 7/898 (0.8%) reported for LEC10-BW (Table 62). Of the genotypes, homozygous *APOE4* carriers had a higher incidence of serious ARIA-E (3/141 [2.1%]) compared to noncarriers (2/278 [0.7%]) and heterozygous *APOE4* carriers (2/479 [0.4%]). In the Noncarrier and Heterozygous *APOE4* Carrier Population 4/757 (0.5%) LEC10-BW subjects had serious ARIA-E.

Table 62. Treatment-emergent serious adverse events due to ARIA-E – study 301 core (safety analysis set)

Population	Placebo n/m (%)	Lecanemab 10 mg/kg Biweekly n/m (%)
Overall	0	7/898 (0.8)
Noncarrier and Heterozygous *APOE4* Carriers	0	4/757 (0.5)
Individual Genotype		
Noncarriers	0	2/278 (0.7)
Heterozygous *APOE4* Carriers	0	2/479 (0.4)
Homozygous *APOE4* Carriers	0	3/141 (2.1)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid related imaging abnormality oedema/effusion, m = number of subjects in each category, n = number of subjects with an event in each category.
Source: Study 301 Core CSR Table 14.3.2.6.10.1.

Study 301 Open Label Extension (36 Months Total Treatment)

There were 19/1616 (1.2%) treatment-emergent serious ARIA-E reported in the LEC10-BW Treated Period (Table 63). The rate was higher in homozygous APOE4 carriers (9/250 [3.6%]) compared to noncarriers (4/497 [0.8%]) and heterozygous *APOE* carriers (6/869 [0.7%]). In the Noncarrier and Heterozygous *APOE4* Carrier Population 10/1366 (0.7%) LEC10-BW subjects had serious ARIA-E.

Table 63. Incidence of treatment-emergent serious ARIA-E – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	LEC10-BW n (%)
Overall	19/1616 (1.2)
Noncarrier and Heterozygous *APOE4* Carriers	10/1366 (0.7)
Individual Genotype	
Noncarriers	4/497 (0.8)
Heterozygous *APOE4* Carriers	6/869 (0.7)
Homozygous *APOE4* Carriers	9/250 (3.6)

LEC10-BW-Treated Period includes Core Study and OLE Phase in which subjects received LEC10-BW. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received LEC10-BW from the OLE Phase, and is the Core Study baseline for subjects who received LEC10-BW from the Core Study. A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.
If a subject had two or more ARIAs with different severities, then the event with the maximum severity was used for that subject. Data collected after subjects switch to/start subcutaneous dose are not included.
AE = adverse event, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, *APOE4* = apolipoprotein E4 variant, ARIAs = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, OLE = open-label extension, TEAE = treatment-emergent adverse event.
Source: Appendix 1 sCSR5 Table 14.3.2.6.10.1a.

Postmarketing Experience (up to 18 Months Experience)

In addition, the applicant provided a Pharmacovigilance summary for the re-examination procedure.

There have been 25 serious events of ARIA-E and 8 serious reports of ARIA without further description regarding the type of ARIA. Among the serious reports, 52% (13/25) did not require hospitalisation.

The majority of serious reports of ARIA-E were symptomatic (68%) and occurred early in treatment with all occurring prior to the 14th dose of lecanemab. The most commonly reported symptoms were headache and confusion, although more serious symptoms, including seizures, have been reported. Radiographic severity was mild in 4 events, moderate in 1 event, and severe in 3 events. For the remaining events, radiographic severity was not known. There were no reports of serious ARIA-E in

noncarriers, 8 in heterozygous *APOE4* carriers, and 6 in homozygous *APOE4* carriers. For the remaining events, *APOE4* status was not known.

There were 3 reports of deaths in patients who experienced ARIA-E, 2 of which were concurrent with ARIA-H, which are discussed in Section 0.

While the number of patients treated commercially with lecanemab is not known, and the reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, the rate of serious ARIA-E (based on an estimated reporting rate of 0.008 per patient-year of exposure) is consistent with that observed in the clinical development programme.

The incidence of serious ARIA-E in the Japanese postmarketing data was 0.2%. Of note, at this time *APOE4* genotype data is limited due to access to *APOE4* testing in Japan.

The majority of serious reports of ARIA-E were symptomatic and occurred early in treatment with all occurring prior to the 6th dose of lecanemab. The most commonly reported symptoms were headache, confusion and alterations of consciousness, although more serious symptoms, including seizures, have occurred. Radiographic severity was known in 2 reports, with 1 report each of moderate and severe radiographic severity.

(3) Symptomatic ARIA-E

The applicant provided analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

In Study 301 Core, in the Overall Population, 25/898 (2.8%) LEC10-BW subjects had treatment-emergent symptomatic ARIA-E (Table 64). Of the genotypes, homozygous *APOE4* carriers (13/141 [9.2%]) had a higher incidence of symptomatic ARIA E compared to noncarriers (4/278 [1.4%]) and heterozygous *APOE4* carriers (8/479 [1.7%]). In the Noncarrier and Heterozygous *APOE4* Carrier Population, 12/757 (1.6%) LEC10-BW subjects had symptomatic ARIA-E.

Table 64. Treatment-emergent symptomatic ARIA-E – study 301 core (safety analysis set)

Population	**Placebo n/m (%)**	**Lecanemab 10 mg/kg Biweekly n/m (%)**
Overall	0	25/898 (2.8)
Noncarrier and Heterozygous *APOE4* Carriers	0	12/757 (1.6)
Individual Genotype		
Noncarriers	0	4/278 (1.4)
Heterozygous *APOE4 carrier*	0	8/479 (1.7)
Homozygous *APOE4 carrier*	0	13/141 (9.2)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, m = number of subjects in each category, n = number of subjects with an event in each category.
Source: Appendix 1 Table 14.3.2.6.16 and Study 301 Core CSR Table 14.3.2.6.10.3.

In the Overall Population, symptoms of treatment-emergent ARIA-E were similar across genotypes, with the most common symptoms reported as

- Headache was reported in 12 (1.3%) subjects: 3 were noncarriers, 3 were heterozygous *APOE4* carriers, and 6 were homozygous *APOE4* carriers.

- Confusional state was reported in 4 (0.4%) subjects: 1 was a noncarrier, 1 was a heterozygous *APOE4* carrier, and the remaining 2 were homozygous *APOE4* carriers.
- Dizziness was reported in 3 (0.3%) subjects: 1 was a heterozygous *APOE4* carrier and 2 were homozygous *APOE4* carriers.
- Nausea was reported in 3 (0.3%) subjects: 1 was a heterozygous *APOE4* carrier and 2 were homozygous *APOE4* carriers.

The majority of treatment-emergent symptomatic ARIA-E were mild to moderate (Table 65).

Table 65. Severity of treatment-emergent symptomatic ARIA-E – study 301 core (safety analysis set)

	Placebo n/m (%)			**Lecanemab 10 mg/kg Biweekly n/m (%)**		
	Clinical Severity			**Clinical Severity**		
Population	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Overall	0	0	0	10/898 (1.1)	12/898 (1.3)	3/898 (0.3)
Noncarrier and Heterozygous *APOE4* Carriers	0	0	0	5/757 (0.7)	5/757 (0.7)	2/757 (0.3)
Individual Genotype						
Noncarriers[a]	0	0	0	1/278 (0.4)	3/278 (1.1)	0
Heterozygous *APOE4* Carriers[b]	0	0	0	4/479 (0.8)	2/479 (0.4)	2/479 (0.4)
Homozygous *APOE4* Carriers[c]	0	0	0	5/141 (3.5)	7/141 (5.0)	1/141 (0.7)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid related imaging abnormality oedema/effusion, m = number of subjects in each category, n = number of subjects with an event in each category.
a: Among all noncarriers in the lecanemab group with symptomatic ARIA-E (n=4), the distribution was 1/4 (25.0%) mild and 3/4 (75.0%) moderate.
b: Among all heterozygous *APOE4* carriers in the lecanemab group with symptomatic ARIA-E (n=8), the distribution was 4/8 (50.0%) mild, 2/8 (25.0%) moderate, and 2/8 (25.0%) severe.
c: Among all homozygous *APOE4* carriers in the lecanemab group with symptomatic ARIA-E (n=13), the distribution was 5/13 (38.5%), 7/13 (53.8%), and 1/13 (7.7%).
Source: Appendix 1 Table 14.3.2.6.15 and Study 301 Core CSR Table 14.3.2.6.15.

In the Overall Population, the 3 subjects with severe ARIA-E symptoms (2 were heterozygous *APOE4* carriers and 1 was a homozygous *APOE4* carrier) reported the following symptoms (Study 301 Core CSR Listing 16.2.7.5):

- Aphasia, hyporesponsive to stimuli: 1 subject (Subject 1602-1013; heterozygous *APOE4* carrier)
- Generalized tonic-clonic seizure: 1 subject (Subject 2306-1015; heterozygous *APOE4* carrier)
- Partial seizures with secondary generalisation and vision blurred: 1 subject (Subject 2205-1023; homozygous *APOE4* carrier).

Study 301 Open Label Extension (36 Months Total Treatment)

Consistent with what was reported for the Core, in the LEC10-BW Treated Period few (3.6%) subjects in the Overall Population reported treatment-emergent symptomatic ARIA-E, with homozygous *APOE4* carriers having a higher rate of symptomatic ARIA-E (30/250 [12.0%]) compared to noncarriers (9/497 [1.8%]) and heterozygous *APOE4* carriers (19/869 [2.2%]) (Table 66). In the Noncarrier and Heterozygous *APOE4* Carrier Population, 2.0% of subjects reported symptomatic ARIA-E.

Table 66. Treatment-emergent symptomatic ARIA-E – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	**Lecanemab 10 mg/kg Biweekly n/m (%)**
Overall	58/1616 (3.6)
Noncarrier and Heterozygous *APOE4* Carriers	28/1366 (2.0)
Individual Genotype	
Noncarriers	9/497 (1.8)
Heterozygous *APOE4 carrier*	19/869 (2.2)
Homozygous *APOE4 carrier*	30/250 (12.0)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid related imaging abnormality oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category, n = number of subjects with an event in each category, OLE = open-label extension.
Source: Appendix 1 sCSR5 Table 14.3.2.6.15a.

In the LEC10-BW-Treated Set, in the Overall Population, the most common symptoms reported were (Appendix 1 sCSR5 Table 14.3.2.6.16a, Appendix 1 Listing 16.2.7.1, and Appendix 1 Listing 16.2.7.5):

- Headache was reported in 28 (1.7%) subjects (this includes the 12 subjects from Study 301 Core): 5 were noncarriers, 9 were heterozygous *APOE4* carriers, and 14 were homozygous *APOE4* carriers.
- Confusional state was reported in 12 (0.7%) subjects (this includes the 4 subjects from Study 301 Core): 3 were noncarriers, 4 were heterozygous *APOE4* carriers, and 5 were homozygous *APOE4* carriers.
- Nausea was reported in 4 (0.2%) subjects (this includes the 3 subjects from Study 301 Core): 0 were noncarriers, 2 were heterozygous *APOE4* carriers, and 2 were homozygous *APOE*4 carriers.
- Dizziness was reported in 3 (0.2%) subjects (all subjects reported this symptom in the Core): 0 were noncarriers, 1 was a heterozygous *APOE4* carrier, and 2 were homozygous *APOE4* carriers.
- Aphasia was reported in 3 (0.2%) subjects: 0 were noncarriers, 2 were heterozygous *APOE4* carriers, and 1 was a homozygous *APOE4* carrier.

Consistent with what was reported in the Core, in the LEC10-BW Treated Period the majority of symptomatic ARIA-E was mild to moderate, with few LEC10-BW subjects reporting severe symptomatic ARIA-E, irrespective of genotype (Table 67).

Table 67. Severity of treatment-emergent symptomatic ARIA-E – study 301 OLE – LEC10-BW-treated period (safety analysis set)

	Lecanemab 10 mg/kg Biweekly		
	Clinical Severity **n/m (%)**		
Population (n, %)	**Mild**	**Moderate**	**Severe**
Overall	24/1616 (1.5)	23/1616 (1.4)	11/1616 (0.7)
Noncarrier and Heterozygous *APOE4* Carriers	11/1366 (0.8)	11/1366 (0.8)	6/1366 (0.4)
Individual Genotype			
Noncarriers	3/497 (0.6)	5/497 (1.0)	1/497 (0.2)
Heterozygous *APOE4* Carriers	8/869 (0.9%)	6/869 (0.7)	5/869 (0.6)
Homozygous *APOE4* Carriers	13/250 (5.2)	12/250 (4.8)	5/250 (2.0)

AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, LEC10-BW = lecanemab 10 mg/kg biweekly, OLE = open-label extension, TEAE = treatment-emergent adverse event. LEC10-BW-Treated Period includes Core Study and OLE Phase in which subjects received lecanemab 10 mg/kg Biweekly. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received placebo in the Core Study, and is the Core Study baseline for subjects who received lecanemab 10 mg/kg Biweekly in the Core Study. A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. If a subject had two or more ARIAs with different severities, then the event with the maximum severity was used for that subject. The severity under asymptomatic period is not considered. Data collected after subjects switch to/start subcutaneous dose are not included.
Source: Appendix 1 sCSR5 Table 14.3.2.6.15a.

In the LEC10-BW-treated set, in the Overall Population 8 subjects newly reported severe symptoms since the Core, which included:

- Seizure, gait disturbance, confusional state: 1 subject (heterozygous *APOE4* carrier)
- Seizure, hemiplegia, dysarthria: 1 subject (homozygous *APOE4* carrier)
- Confusional state, aphasia, seizure: 1 subject (heterozygous *APOE4* carrier)
- Hemiparesis: 1 subject (homozygous *APOE4* carrier)
- Impaired reasoning, bradyphenia, hemianopia homonymous: 1 subject (*APOE4* noncarrier)
- Headache, hemianopia homonymous, focal dyscognitive seizures, visual perseveration, electroencephalogram abnormal, hallucination visual, visual impairment: 1 subject (homozygous *APOE4* carrier)
- Headache, aphasia, confusional state: 1 subject (homozygous *APOE4* carrier)
- Seizure, headache: 1 subject (heterozygous *APOE4* carrier

Postmarketing Experience (up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

There have been 38 symptomatic events of ARIA-E and 8 reports of ARIA without further description provided regarding the type of ARIA.

Consistent with the description of symptomatic ARIA in the proposed SmPC, symptoms were generally mild to moderate with the most commonly reported symptoms being headache and confusion. Additional symptoms associated with ARIA included vision changes, dizziness/balance issues, memory loss, and tiredness, although more severe symptoms including seizures have also been reported.

Symptomatic reports of ARIA-E occurred early in treatment with all occurring prior to the 14th dose of lecanemab. Radiographic severity was mild in 3 events, moderate in 6 events, and severe in 3 events. For the remaining events, radiographic severity was not known. There were 2 reports of symptomatic ARIA-E in *APOE4* noncarriers, 4 in heterozygous *APOE4* carriers, and 10 in homozygous *APOE4* carriers. For the remaining events, *APOE4* status was not known.

While the number of patients treated commercially with lecanemab is not known and the reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, the rate of symptomatic ARIA-E (based on an estimated reporting rate of 0.01 per patient-year of exposure) is consistent with that observed in the clinical development programme.

The incidence of symptomatic ARIA-E in the Japanese postmarketing data was 0.2%. Of note, *APOE4* genotype data is limited due to access to *APOE4* testing in Japan.

The majority of reports of symptomatic ARIA-E were serious and occurred early in treatment with all occurring prior to the 6th dose of lecanemab. The most commonly reported symptoms were headache, confusion, and alterations of consciousness, although more serious symptoms, including seizures, have occurred. Radiographic severity was known in 2 reports, both of which were of severe radiographic severity.

5.1.1.3.4. ARIA-H

ARIA-H occurs spontaneously in AD in the absence of anti-amyloid therapies due to underlying amyloid infiltration and resulting friability of cerebral blood vessels (CAA). In AD clinical studies, the rate of ARIA-H in PBO ranges from 8.6% – 13.6%, and is as high as 21% in homozygous *APOE4* subjects (Honig, et al., 2024).

ARIA-H is typically characterized as cerebral microhaemorrhages and superficial siderosis. For both, ARIA-H cerebral microhaemorrhages and ARIA-H superficial siderosis, the number of areas affected determines severity. ARIA-H is an MRI radiographic finding detected incidentally on routine MRI surveillance and is typically asymptomatic. ARIA-H occurs in 3 settings: 1) overall ARIA-H, 2) isolated ARIA-H not associated with ARIA-E and, 3) ARIA-H concurrent with ARIA-E. The excess in overall ARIA-H for LEC10-BW relative to PBO is due to ARIA-H that occurs concurrent with ARIA-E, with timing and clinical characteristics reflective of the ARIA-E, as described in Section 5.1.1.3.3. . The incidence and timing of isolated ARIA-H are similar for PBO and LEC10-BW. Therefore, this section will describe first the incidence of overall ARIA-H, then isolated ARIA-H, and ARIA-H concurrent with ARIA-E discussed as appropriate.

Similar to ARIA-E, risk factors for ARIA-H are CAA and cerebral microhaemorrhages (Ulrich et al., 2018; Piazza, et al., 2022). Increasing number of APOE4 alleles is also a risk factor for ARIA-H, as the presence of alleles is associated with increased cerebral amyloid deposition in blood vessel walls (Antolini, et al., 2021). Subjects with *APOE4* alleles have higher risks of CAA and cerebral microhaemorrhages (Ulrich, et al., 2018; Piazza, et al., 2022), irrespective of whether they receive anti-amyloid therapy.

In Study 301 Core, for the Overall Population, the incidence of isolated ARIA-H was lower in PBO (69/897 [7.7%]) (0.0560 per patient-year of exposure) than LEC10-BW (78/898 [8.7%]) (0.0662 per patient-year of exposure). Of the genotypes, homozygous *APOE4* carriers had a higher incidence of isolated ARIA-H even in the absence of treatment (24/133 [18.0%] PBO, 17/141 [12.1%] LEC10-BW). When homozygous *APOE4* carriers are removed from the analyses (Noncarrier and Heterozygous *APOE4* Carrier Population) the incidence was 45/764 (5.9%) subjects on PBO (0.0430 per patient-year of exposure) and 61/757 (8.1%) subjects on LEC10-BW (0.0612 per patient-year of exposure).

In the OLE Phase ("LEC10-BW Treated Period" which represents all subjects treated with LEC10-BW in the Core and OLE Phase), the incidence of overall ARIA-H in the LEC10-BW Treated Period for the Overall Population remained consistent with the Core, with the slight increase in ARIA-H (16.9% Core, 23.8% LEC10-BW Treated Period) due to Core PBO-treated subjects receiving LEC10-BW for the first time in the OLE Phase. In the Noncarrier and Heterozygous *APOE4* Carrier Population the incidence was 166/1366 (12.2%) (0.0558 per patient-year of exposure).

Across both the Core and OLE Phase, isolated ARIA-H was distributed throughout the treatment period for both PBO and LEC10-BW, irrespective of genotype. ARIA-H does not typically resolve radiographically, as hemosiderin deposition is typically not reabsorbed.

Most isolated ARIA-H was asymptomatic, in the Core the incidence of symptomatic ARIA-H in the Noncarrier and Heterozygous *APOE4* Carrier Population was low, 2/757 (0.3%), and events were mostly mild-to-moderate in severity. The most common symptoms were headache, confusional state, and dizziness. There were no severe events reported.

In response to CHMP questions, the applicant evaluated concomitant anticoagulant and/or antiplatelet use and the risk of ARIA-H. In Study 301 Core, the incidence of ARIA-H with LEC10-BW treatment is lower following antiplatelet or anticoagulant use. The use of antiplatelets and anticoagulants demonstrated no increased incidence of ARIA -H when used with LEC10-BW versus LEC10-BW alone.

In the Core, there were no deaths on LEC10-BW and 1 death (0.0008 per patient-year of exposure) with concurrent ICH>1 cm in PBO: 1 (noncarrier) subject. In the OLE Phase, there were 3 deaths (0.0009 per patient-year of exposure) with concurrent ARIA-E, -H, or ICH> 1 cm: 1 (homozygous APOE4 carrier) subject with multiple ICH>1 cm after tissue plasminogen activator (tPA); 1 (noncarrier) subject with subacute ICH>1 cm; and 1 (homozygous APOE4 carrier) subject with severe ARIA-E and concurrent ARIA-H microhaemorrhage. Overall, deaths, and deaths with concurrent ARIA, when adjusted to patient-years of exposure, are similar for LEC10-BW and PBO.

Available postmarketing experience (up to 18 months) indicates that the rate of ARIA-H reported is consistent with that observed clinical development programme.

The proposed SmPC indication excludes homozygous *APOE4* carriers and provides details for physicians regarding the detection and clinical management of patients who experience ARIA-H events. The Applicant has also proposed a number of activities to support HCPs in the monitoring for these events and to ensure HCPs are aware of appropriate patient management if these events occur. Pharmacovigilance activities including a follow up questionnaire to be used by HCPs when reporting postmarketing ARIA-H events as well as a PASS to further characterize ARIA-E, -H and ICH>1 cm, effectiveness of RMMs, and drug utilisation are also planned.

The ARIA-H summary that follows contains both previously submitted and new analyses, with new analyses or content identified

The long-term consequences of ARIA-H is discussed in 5.1.1.3.9. .

(1) Incidence and Radiographic Severity of ARIA-H

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo Controlled Treatment)

There is a high background rate of ARIA-H in AD, as evidenced by PBO rates in Study 301 Core.

In Study 301 Core, the incidence of treatment-emergent overall ARIA-H was lower in PBO than LEC10-BW (Table 68). Of the genotypes, homozygous *APOE4* carriers had a higher incidence of ARIA-H even in the absence of treatment (PBO 28/133 [21.1%] subjects; LEC10-BW 54/141 [38.3%] subjects) compared to noncarriers (PBO 11/286 [3.8%] subjects; LEC10-BW 32/278 [11.5%] subjects) and heterozygous *APOE4* carriers (PBO 41/478 [8.6%] subjects; LEC10-BW 66/479 [13.8%] subjects).

The incidence of isolated ARIA-H was similar for PBO and LEC10-BW. Of the genotypes, homozygous *APOE4* carriers had a higher incidence of isolated ARIA-H even in the absence of treatment (PBO 24/133 [18.0%] subjects; LEC10-BW 17/141 [12.1%] subjects) compared to noncarriers (PBO 10/286 [3.5%] subjects; LEC10-BW 22/278 [7.9%] subjects) and heterozygous *APOE4* carriers (PBO 35/478 [7.3%] subjects; LEC10-BW 39/479 [8.1%] subjects).

Table 68. Incidence of treatment-emergent ARIA-H (overall and isolated) – study 301 core (safety analysis set)

Population (n, %)	**Placebo n/m (%)**	**Lecanemab 10 mg/kg Biweekly n/m (%)**
Overall ARIA-H		
Overall	80/897 (8.9)	152/898 (16.9)
Noncarrier and Heterozygous *APOE4* Carriers	52/764 (6.8)	98/757 (12.9)
Individual Genotype		
Noncarriers	11/286 (3.8)	32/278 (11.5)
Heterozygous *APOE4* Carriers	41/478 (8.6)	66/479 (13.8)
Homozygous *APOE4* Carriers	28/133 (21.1)	54/141 (38.3)
Isolated ARIA-H		
Overall	69/897 (7.7)	78/898 (8.7)
Noncarrier and Heterozygous *APOE4* Carriers	45/764 (5.9)	61/757 (8.1)
Individual Genotype		
Noncarriers	10/286 (3.5)	22/278 (7.9)
Heterozygous *APOE4* Carriers	35/478 (7.3)	39/479 (8.1)
Homozygous *APOE4* Carriers	24/133 (18.0)	17/141 (12.1)

APOE4 = apolipoprotein E4 variant, ARIA-H = amyloid-related imaging abnormality- haemorrhage, N = number of subjects in treatment group, n = number of subjects with an event in each category, PBO = placebo, m = number of subjects in each category, TEAE = treatment emergent adverse event.
Source: Appendix 1 Table 14.3.2.6.10.2nh and Appendix 1 14.3.2.6.10nh.

Figure 30 shows that isolated ARIA-H events in PBO and LEC10-BW were distributed over the course of treatment and occurred at a similar rate.

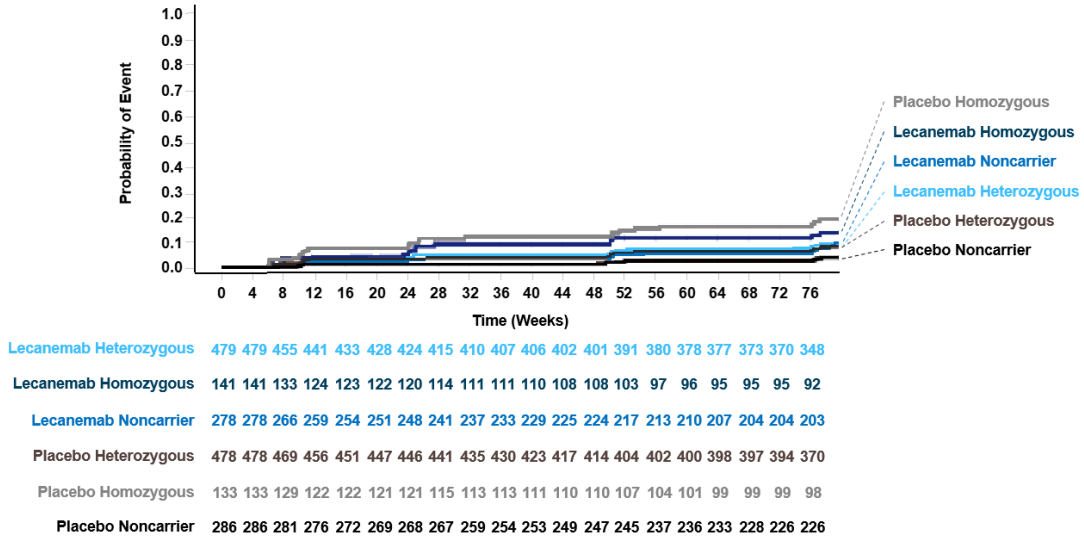


Figure 30. Kaplan-Meier curves for time to first isolated ARIA-H in the overall population by APOE4 genotype – study 301 core (safety analysis set)

APOE4 = apolipoprotein E4 variant, ARIA-H = amyloid-related imaging abnormality- haemorrhage.
Source: Appendix 1 Figure 14.3.2.6.2.2nh.

The majority of isolated ARIA-H were mild to moderate radiographically (Table 69), which was consistent across all genotypes. ARIA-H does not typically resolve radiographically, as hemosiderin deposition is typically not reabsorbed.

Table 69. Radiographic severity of treatment-emergent ARIA-H (overall and isolated) – study 301 core (safety analysis set)

Population	**Placebo n/m (%)**			**Lecanemab 10 mg/kg Biweekly n/m (%)**		
	Radiographic Severity			**Radiographic Severity**		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Overall ARIA-H						
Overall	73/897 (8.1)	5/897 (0.6)	2/897 (0.2)	97/898 (10.8)	24/898 (2.7)	31/898 (3.5)
Noncarrier and Heterozygous *APOE4* Carriers	49/764 (6.4)	1/764 (0.1)	2/764 (0.3)	75/757 (9.9)	11/757 (1.5)	12/757 (1.6)
Individual Genotype						
Noncarriers[a]	10/286 (3.5)	0	1/286 (0.3)	27/278 (9.7)	2/278 (0.7)	3/278 (1.1)
Heterozygous *APOE4* Carriers[b]	39/478 (8.2)	1/478 (0.2)	1/478 (0.2)	48/479 (10.0)	9/479 (1.9)	9/479 (1.9)
Homozygous *APOE4* Carriers[c]	24/133 (18.0)	4/133 (3.0)	0	22/141 (15.6)	13/141 (9.2)	19/141 (13.5)
Isolated ARIA-H						
Overall	66/897 (7.4)	3/897 (0.3)	0	67/898 (7.5)	9/898 (1.0)	2/898 (0.2)
Noncarrier and Heterozygous *APOE4* Carriers	44/764 (5.8)	1/764 (0.1)	0	54/757 (7.1)	5/757 (0.7)	2/757 (0.3)
Individual Genotype						
Noncarriers[d]	10/286 (3.5)	0	0	20/278 (7.2)	1/278 (0.4)	1/278 (0.4)
Heterozygous *APOE4* Carriers[e]	34/478 (7.1)	1/478 (0.2)	0	34/479 (7.1)	4/479 (0.8)	1/479 (0.2)
Homozygous *APOE4* Carriers[f]	22/133 (16.5)	2/133 (1.5)	0	13/141 (9.2)	4/141 (2.8)	0

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality haemorrhage, m = number of subjects in each category, n = number of subjects with an event in each category.
a: Overall ARIA-H – among all noncarriers in the lecanemab group with radiographic ARIA-H (n=32), the distribution was 27/32 (84.4%) mild, 2/32 (6.3%) moderate, and 3/32 (9.4%) severe.
b: Overall ARIA-H – among all heterozygous *APOE4* carriers in the lecanemab group with radiographic ARIA-H (n=66), the distribution was 48/66 (72.7%) mild, 9/66 (13.6%) moderate, and 9/66 (13.6%) severe.
c: Overall ARIA-H – among all homozygous *APOE4* carriers in the lecanemab group with radiographic ARIA-H (n=54), the distribution was 22/54 (40.7%) mild, 13/54 (24.1%) moderate, and 19/54 (35.2%) severe.
d: Isolated – among all noncarriers in the lecanemab group with radiographic ARIA-H (n=22), the distribution was 20/22 (91.0%) mild, 1/22 (4.5%) moderate, and 1/22 (4.5%) severe.
e: Isolated – among all heterozygous *APOE4* carriers in the lecanemab group with radiographic ARIA-H (n=39), the distribution was 34/39 (87.2%) mild, 4/39 (10.3%) moderate, and 1/39 (2.6%) severe.
f: Isolated – among all homozygous *APOE4* carriers in the lecanemab group with radiographic ARIA-H (n=17), the distribution was 13/17 (76.5%) mild and 4/17 (23.5%) moderate.
Source: Appendix 1 Table 14.3.2.6.10.2nh and Appendix 1 Table 14.3.2.6.10.6nh.

Study 301 OLE (36 Months Total Treatment)

Data presented for Study 301 OLE Phase are cumulative for any subject who received at least 1 dose of LEC10-BW at any time, whether in the Core Study or OLE Phase (data cutoff 31 Mar 2024) (i.e., LEC10-BW Treated Period). Therefore, these data are a pooled presentation of all LEC10-BW treated subjects across the total duration of Study 301. Data presented for the OLE Phase reflect up to 36 months treatment with LEC10-BW.

The overall incidence of treatment-emergent ARIA-H (overall, isolated, and concurrent with ARIA-E) in the LEC10-BW Treated Period (Table 70) remained consistent with the Core, with the slight increase in ARIA-H (Overall Population; overall ARIA-H: 16.9% Core, 23.8% LEC10-BW Treated Period, isolated ARIA-H: 8.7% Core, 13.1% LEC10-BW Treated Period and Noncarrier and Heterozygous *APOE4* Carrier

Population; overall ARIA-H 12.9% Core, 19.3% LEC10-BW Treated Period, isolated ARIA-H 8.1% Core, 12.2% LEC10-BW Treated Period) due to Core PBO-treated subjects receiving LEC10-BW for the first time in the OLE Phase. The incidence of ARIA-H with longer-term treatment was similar to the Core when assessed by genotype.

Table 70. Incidence of treatment-emergent ARIA-H (overall, isolated and concurrent with ARIA-E) – study 301 OLE – LEC10-BW-treated period (safety analysis set)

ARIA Term	LEC10-BW (N=1616) n/m (%)
Overall ARIA-H	
Overall	385 (23.8)
Noncarrier and Heterozygous *APOE4* Carriers	264/1366 (19.3)
Individual Genotype	
Noncarriers	82/497 (16.5)
Heterozygous *APOE4* Carriers	182/869 (20.9)
Homozygous *APOE4* Carriers	121/250 (48.4)
Isolated ARIA-H	
Overall	211 (13.1)
Noncarrier and Heterozygous *APOE4* Carriers	166/1366 (12.2)
Individual Genotype	
Noncarriers	60/497 (12.1)
Heterozygous *APOE4* Carriers	106/869 (12.2)
Homozygous *APOE4* Carriers	45/250 (18.0)
Concurrent ARIA-H and ARIA-E[b]	
Overall	164 (10.1)
Noncarrier and Heterozygous *APOE4* Carriers	93/1366 (6.8)
Individual Genotype	
Noncarriers	21/497 (4.2)
Heterozygous *APOE4* Carriers	72/869 (8.3)
Homozygous *APOE4* Carriers	71/250 (28.4)

LEC10-BW-Treated Period includes Core Study and OLE Phase in which subjects received LEC10-BW. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received LEC10-BW from the OLE Phase, and is the Core Study baseline for subjects who received LEC10-BW from the Core Study. ARIA-H is defined as events of superficial siderosis or cerebral microhaemorrhage. A TEAE is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. A subject with two or more events is counted only once for that event. *APOE4* carrier and noncarrier status and genotype are based on actual lab data. n = number of subjects with an event in each category. The percentage is calculated as n/m*100. Data collected after subjects switch to/start subcutaneous dose are not included.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category; OLE = open-label extension, TEAE = treatment-emergent adverse event.
a: Subjects with at least one ARIA-E event and at least one ARIA-H event during the study, not necessarily concurrent.
b: Concurrent is defined as overlapping in the AE duration of 2 ARIA events.
Source: Appendix 1 sCSR5 Table 14.3.2.6.10a.

A longer period of follow-up in the OLE Phase (up to 36 months) continues to show that ARIA-H occurs across the treatment period. In Study 301 OLE Phase MRIs were conducted at OLE baseline, Week 11, 15, 27 then every 6 months per protocol due to Core PBO subjects receiving LEC10-BW for the first time (Figure 31).

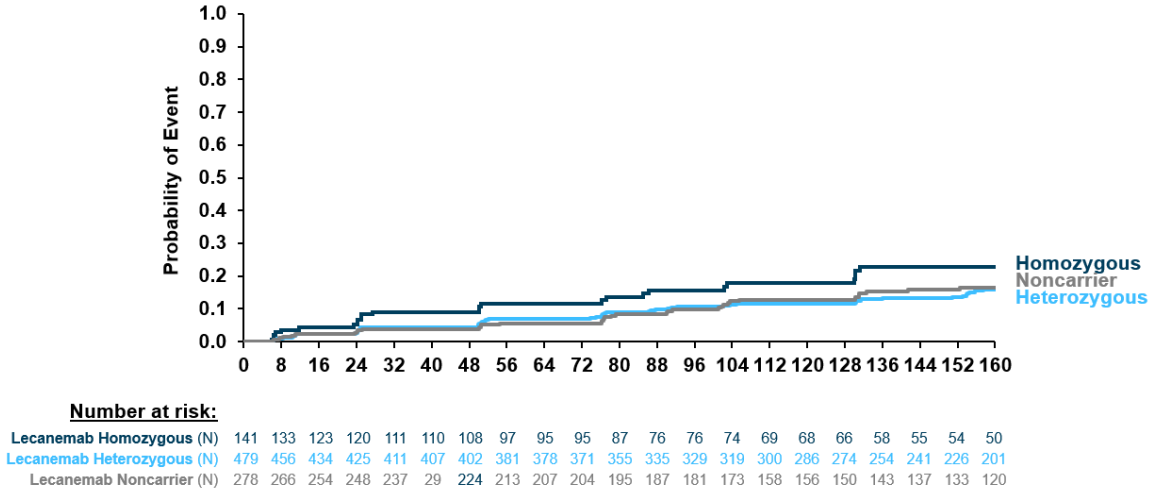


Figure 31. Kaplan-Meier curves for time to first isolated ARIA-H in core lecanemab group by APOE4 genotype – study 301 core and OLE phase (safety analysis set)

APOE4 = apolipoprotein E4 variant, ARIA-H = amyloid related imaging abnormality haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, OLE = open-label extension.
Source: Appendix 1 Figure 14.3.2.6.4.2.

Consistent with the Core, the majority of overall and isolated ARIA-H was mild to moderate radiographically (Table 71), which was consistent across all genotypes.

Table 71. Radiographic severity of treatment-emergent ARIA-H (overall and isolated) – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	**Lecanemab 10 mg/kg Biweekly n/m (%)**		
	Radiographic Severity		
	Mild	**Moderate**	**Severe**
Overall ARIA-H			
Overall	248/1616 (15.3)	60/1616 (3.7)	76/1616 (4.7)
Noncarrier and Heterozygous *APOE4* Carriers	190/1366 (13.9)	39/1366 (2.9)	34/1366 (2.5)
Individual Genotype			
Noncarriers	68/497 (13.7)	6/497 (1.2)	7/497 (1.4)
Heterozygous *APOE4* Carriers	122/869 (14.0)	33/869 (3.8)	27/869 (3.1)
Homozygous *APOE4* Carriers	58/250 (23.2)	21/250 (8.4)	42/250 (16.8)
Isolated ARIA-H			
Overall	178/1616 (11.0)	21/1616 (1.3)	12/1616 (0.7)
Noncarrier and Heterozygous *APOE4* Carriers	141/1366 (10.3)	17/1366 (1.2)	8/1366 (0.6)
Individual Genotype			
Noncarriers	53/497 (10.7)	4/497 (0.8)	3/497 (0.6)
Heterozygous *APOE4* Carriers	88/869 (10.1)	13/869 (1.5)	5/869 (0.6)
Homozygous *APOE4* Carriers	37/250 (14.8)	4/250 (1.6)	4/250 (1.6)

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, m = number of subjects in each category, n = number of subjects with an event in each category.
Source: Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.10.2a and Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.10.6a.

Postmarketing Experience (up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

The following PTs were used for ARIA-H: amyloid related imaging abnormalities – microhaemorrhages and haemosiderin deposits, superficial siderosis of central nervous system and cerebral microhaemorrhage.

There have been 100 events of ARIA-H (microhaemorrhage or superficial siderosis) reported

While the relative proportion of serious and symptomatic spontaneous and solicited reports was higher than that observed in Study 301, it would be expected that serious and symptomatic cases are more likely to be reported spontaneously than asymptomatic cases. Additionally, the solicited reports are largely from patient support programs which are more likely to receive information about lecanemab interruptions and are therefore more likely to be more severe events.

The majority of reports of ARIA-H (cerebral microhaemorrhage and superficial siderosis) were nonserious (85%) and asymptomatic (74%). ARIA-H was concurrent with ARIA-E in 52% of reports. When the radiographic severity was known, the majority of reports were mild to moderate in severity (39/48, 81%). When *APOE4* genotype was known, 18% (9/50) of ARIA-H occurred in noncarriers, 50% (25/50) in heterozygous *APOE4* carriers, and 32% (16/50) in homozygous *APOE4* carriers. There were 11 reports of ARIA-H in which the patient was receiving a concomitant antiplatelet agent, most of which were aspirin, and no reports of ARIA-H in which the patient was concomitantly taking an anticoagulant or had received a thrombolytic.

Acknowledging the limitations of spontaneous reporting and that the specific number of patients treated commercially with lecanemab is not known and a reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, the rate (based on an estimated reporting rate of 0.03 per patient-year of exposure) and severity of ARIA-H, is consistent with that observed in the clinical development programme.

The incidence of ARIA-H (microhaemorrhage and superficial siderosis) in the Japanese postmarketing data was 0.9%. Of note, *APOE4* genotype data is limited due to access to *APOE4* testing in Japan.

All reports of ARIA-H were for cerebral microhaemorrhage. No ARIA-H superficial siderosis was reported. All reports for ARIA-H (cerebral microhaemorrhage) were nonserious and the majority were asymptomatic (95%). ARIA-H was concurrent with ARIA-E in 52% of reports. When the radiographic severity was known, the majority of reports were mild to moderate in severity (83%). There were no reports of ARIA-H in which the patient was receiving a concomitant antiplatelet, anticoagulant, or had received a thrombolytic.

(2) Serious Adverse Events due to ARIA-H

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo Controlled Treatment)

In the Overall Population there were 2/898 (0.2%) treatment-emergent serious ARIA-H reported in the Core, one was concurrent with radiographically moderate symptomatic ARIA-E in a noncarrier on LEC10-BW and the other was concurrent with moderate asymptomatic ARIA-E in a homozygous *APOE4* carrier on LEC10-BW (Study 301 Core CSR).

Study 301 OLE (36 Months Total Treatment)

There were 9/1616 (0.6%) treatment-emergent serious ARIA-H reported in the LEC10-BW Treated Period. Of these 9 subjects with serious ARIA-H, 2 subjects experienced ARIA-H in the Core Study, with the remaining events occurring in the OLE Phase. Serious ARIA-H were higher in homozygous *APOE4*

carriers (5/250 [2.0%] subjects) compared to noncarriers (2/497 [0.4%]) and heterozygous *APOE4* carriers (2/869 [0.2%]). In the Noncarrier and Heterozygous *APOE4* Carrier Population 4/1366 (0.3%) LEC10-BW subjects had serious ARIA-H.

Table 72 provides details of the serious ARIA-H reported in the LEC10-BW Treated Period. All were concurrent with ARIA-E. Increasing number of E4 alleles is a risk factor for serious ARIA-H.

Table 72. Treatment-emergent serious adverse events of ARIA-H - study 301 OLE – LEC10-BW-treated period (safety analysis set)

Subject Identifier	**Isolated ARIA-H or Concurrent with ARIA-E**	***APOE4* Status**	**Hospitalisation**	**Outcome**	**Symptom(s)**
	Concurrent	Noncarrier	Yes	ARIA-H ongoing	left upper extremity weakness along with headache and high blood pressure
	Concurrent	Homozygous *APOE4* Carrier	No	ARIA-H ongoing	No
	Concurrent	Heterozygous *APOE4* Carrier	Yes	ARIA-H Ongoing	Gait disturbances, confusion, and disorientation
	Concurrent	Homozygous *APOE4* Carrier	Yes	Death	Severe seizure, moderate hemiplegia, and moderate dysarthria
	Concurrent	Homozygous *APOE4* Carrier	No	ARIA-H ongoing	No
	Concurrent	Heterozygous *APOE4* Carrier	Yes	ARIA-H and ARIA-E ongoing	ARIA-H: headache and intermittent visual scintillations with onset
	Concurrent	Noncarrier	No	ARIA-H ongoing	No
	Concurrent	Homozygous *APOE4* Carrier	Yes	ARIA-H ongoing	Symptoms associated with ARIA-E: cephalalgia, confusion, visual difficulties, and gait disturbances; associated with ARIA-H: visual impairment
	Concurrent	Homozygous *APOE4* Carrier	Yes	ARIA-H ongoing	Confusion and aphasia

Concurrent is defined as overlapping in the AE duration of 2 ARIA events.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly.
Source: Appendix 1 Study 301 OLE sCSR 5 Listing 16.2.4.1, Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.1, and Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.2.3.

Postmarketing Experience (up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

There have been 15 serious events of ARIA-H (microhaemorrhage or superficial siderosis). Among the serious reports, 73% (11/15) did not require hospitalisation.

The majority of serious reports of ARIA-H (cerebral microhaemorrhage and superficial siderosis) were concurrent with ARIA-E (60%) and symptomatic (67%). The most commonly reported symptoms were headache and confusion, although more serious symptoms, including seizures, have occurred. Radiographic severity was mild in 3 events, moderate in 1 event and severe in 3 events. For the remaining events, radiographic severity was not known. There were no reports of serious ARIA-H in noncarriers, 6 in heterozygous *APOE4* carriers, and 4 in homozygous *APOE4* carriers. For the remaining events, *APOE4* status was not known. There was 1 report of serious ARIA-H in which the patient was

receiving concomitant aspirin and no reports of serious ARIA-H in which the patient was concomitantly taking an anticoagulant or had received a thrombolytic.

There were 2 reports of deaths in patients who experienced ARIA-H, both of which were concurrent with ARIA-E and are discussed below in Section 5.1.1.3.8. .

While the number of patients treated commercially with lecanemab is not known and a reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, considering the estimated exposure of more than 3125 patient-years (estimated exposure based on over 180,000 vials distributed), the rate of serious ARIA-H (based on an estimated reporting rate of 0.005 per patient-year of exposure) is consistent with that observed in the clinical development programme.

There were no serious reports of ARIA-H from the Japanese postmarketing setting.

(3) Symptomatic ARIA-H

Study 301 Core (18 Months Placebo-Controlled Treatment)

In Study 301 Core, in the Overall Population 11/898 (1.2%) LEC10-BW subjects had treatment-emergent symptomatic overall ARIA-H (Table 73). Of the genotypes, the incidence in homozygous *APOE4* carriers was 5/141 (3.5%) compared to noncarriers 2/278 (0.7%) and heterozygous *APOE4* carriers 4/479 (0.8%). In the Noncarrier and Heterozygous *APOE4* Carrier Population 6/757 (0.8%) LEC10-BW subjects had symptomatic overall ARIA-H.

For isolated ARIA-H, in the Overall Population 2/898 (0.2%) LEC10-BW subjects had treatment-emergent symptomatic isolated ARIA-H. There were few events reported, which limits the ability to draw conclusions by genotype: homozygous *APOE4* carriers was 0/141 (0%) compared to noncarriers 0/278 (0%) and heterozygous *APOE4* carriers 2/479 (0.4%). In the Noncarrier and Heterozygous *APOE4* Carrier Population 2/757 (0.3%) LEC10-BW subjects had symptomatic isolated ARIA-H.

Table 73. Treatment-emergent symptomatic ARIA-H (overall and isolated) – study 301 core (safety analysis set)

Population	Placebo n/m (%)	Lecanemab 10 mg/kg Biweekly n/m (%)
Overall ARIA-H		
Overall	2/897 (0.2)	11/898 (1.2)
Noncarrier and Heterozygous *APOE4* Carriers	1/764 (0.1)	6/757 (0.8)
Individual Genotype		
Noncarriers	0/286 (0)	2/278 (0.7)
Heterozygous *APOE4 C*arrier	1/478 (0.2)	4/479 (0.8)
Homozygous *APOE4* Carrier	1/133 (0.8)	5/141 (3.5)
Isolated ARIA-H		
Overall	2/897 (0.2)	2/898 (0.2)
Noncarrier and Heterozygous *APOE4* Carriers	1/764 (0.1)	2/757 (0.3)
Individual Genotype		
Noncarriers	0/286 (0)	0/278 (0)
Heterozygous *APOE4* Carrier	1/478 (0.2)	2/479 (0.4)
Homozygous *APOE4* Carrier	1/133 (0.8)	0/141 (0)

APOE4 = apolipoprotein E4 variant, ARIA-H = amyloid-related imaging abnormality-haemorrhage, m = number of subjects in each category, n = number of subjects with an event in each category.
Source: Study 301 Core CSR Listing 16.2.7.1, and Listing 16.2.7.5; and Appendix 1 Table 14.3.2.6.26nh.

In the Overall Population, symptoms of overall ARIA-H were similar across genotypes, with the most common symptoms reported as:

- Headache was reported in 4/898 (0.4%) subjects: 2 were noncarriers, 1 was a heterozygous *APOE4* carrier, and 1 was a homozygous *APOE4* carrier.
- Dizziness was reported in 3/898 (0.3%) subjects: 2 were heterozygous *APOE4* carriers, and 1 was a homozygous *APOE4* carrier.
- Confusional state was reported in 2/898 (0.2%) subjects: 2 were homozygous *APOE4* carriers.

All treatment-emergent symptomatic overall and isolated ARIA-H were mild to moderate (Table 74). There was no increase in symptomatic severity in homozygous *APOE4* carriers.

Table 74. Severity of treatment-emergent symptomatic ARIA-H (overall and isolated) – study 301 core (safety analysis set)

	Placebo n/m (%)			**Lecanemab 10 mg/kg Biweekly n/m (%)**		
	Clinical Severity			**Clinical Severity**		
Population	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Overall ARIA-H						
Overall	1/897 (0.1)	1/897 (0.1)	0	8/898 (0.9)	3/898 (0.3)	0
Noncarrier and Heterozygous *APOE4* Carriers	0	1/764 (0.1)	0	5/757 (0.7)	1/757 (0.1)	0
Individual Genotype						
Noncarriers[a]	0	0	0	1/278 (0.4)	1/278 (0.4)	0
Heterozygous *APOE4* Carriers[b]	0	1/478 (0.2)	0	4/479 (0.8)	0	0
Homozygous *APOE4* Carriers[c]	1/133 (0.8)	0	0	3/141 (2.1)	2/141 (1.4)	0
Isolated ARIA-H						
Overall	1/897 (0.1)	1/897 (0.1)	0	2/898 (0.2)	0	0
Noncarrier and Heterozygous *APOE4* Carriers	0	1/764 (0.1)	0	2/757 (0.3)	0	0
Individual Genotype						
Noncarriers	0	0	0	0	0	0
Heterozygous *APOE4* Carriers[d]	0	1/478 (0.2)	0	2/479 (0.4)	0	0
Homozygous *APOE4* Carriers	1/133 (0.8)	0	0	0	0	0

APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid related imaging abnormality haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category, n = number of subjects with an event in each category.
a: Overall – among all noncarriers in the lecanemab group with symptomatic ARIA-H (n=2), the distribution was 1/2 (50%) mild and 1/2 (50%) moderate.
b: Overall – among all heterozygous *APOE4* carriers in the lecanemab group with symptomatic ARIA-H (n=4), the distribution was 4/4 mild.
c: Overall – among all homozygous *APOE4* carriers in the lecanemab group with symptomatic ARIA-H (n=5), the distribution was 3/5 (60%) mild and 2/5 (40%) moderate.
d: Isolated – among all heterozygous *APOE4* carriers in the lecanemab group with symptomatic ARIA-H (n=2), the distribution was 2/2 mild.
Source: Appendix 1 Table 14.3.2.6.26nh; Study 301 Core CSR Listing 16.2.7.1, and Study 301 Core CSR Listing 16.2.7.5.

In the Overall Population, no severe overall ARIA-H symptoms were reported (Study 301 Core CSR Listing 16.2.7.5).

Study 301 OLE Study 301 Open Label Extension (36 Months Total Treatment)

Consistent with what was reported for the Core, in the LEC10-BW Treated Period, in the Overall Population 33/1616 (2.0%) LEC10-BW subjects had treatment-emergent symptomatic overall ARIA-H (Table 75). Of the genotypes, the incidence in homozygous APOE4 carriers was 14/250 (5.6%) compared to noncarriers 5/497 (1.0%) and heterozygous *APOE4* carriers 14/869 (1.6%). In the Noncarrier and Heterozygous *APOE4* Carrier Population 19/1366 (1.4%) LEC10-BW subjects had symptomatic overall ARIA-H.

For isolated ARIA-H, in the Overall Population, 8/1616 (0.5%) had treatment-emergent symptomatic isolated ARIA-H. Of the genotypes, the incidence in homozygous *APOE4* carriers was 1/250 (0.4%) compared to noncarriers 2/497 (0.4%) and heterozygous *APOE4* carriers 5/869 (0.6%). In the Noncarrier and Heterozygous *APOE4* Carrier Population, 7/1366 (0.5%) LEC10-BW subjects had symptomatic isolated ARIA-H.

Table 75. Treatment-emergent symptomatic ARIA-H (overall and isolated) – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	Lecanemab 10 mg/kg Biweekly n/m (%)
Overall ARIA-H	
Overall	33/1616 (2.0)
Noncarrier and Heterozygous *APOE4* Carriers	19/1366 (1.4)
Individual Genotype	
Noncarriers	5/497 (1.0)
Heterozygous *APOE4* Carrier	14/869 (1.6)
Homozygous *APOE4* Carrier	14/250 (5.6)
Isolated ARIA-H	
Overall	8/1616 (0.5)
Noncarrier and Heterozygous *APOE4* Carriers	7/1336 (0.5)
Individual Genotype	
Noncarriers	2/497 (0.4)
Heterozygous *APOE4* Carrier	5/869 (0.6)
Homozygous *APOE4* Carrier	1/250 (0.4)

APOE4 = apolipoprotein E4 variant, ARIA-H = amyloid related imaging abnormality haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category, n = number of subjects with an event in each category, OLE = open-label extension.
Source: Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.25a and Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.25.1a.

In the LEC10-BW-Treated Set, in the Overall Population, symptoms of treatment-emergent overall ARIA-H were similar across genotypes, with the most common symptoms reported as follows (Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.27.1a, Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.1, and Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.5):

- Headache was reported in 14 (0.9%) subjects: 3 were noncarriers, 5 were heterozygous *APOE4* carriers, and 6 were homozygous *APOE4* carriers.
- Confusional state was reported in 7 (0.4%) subjects: 1 was a noncarrier, 2 were heterozygous *APOE4* carriers, and 4 were homozygous *APOE4* carriers.
- Dizziness was reported in 5 (0.3%) subjects: 4 were heterozygous *APOE4* carriers and 1 was a homozygous *APOE4* carrier.

Consistent with what was reported in the Core, in the LEC10-BW Treated Period the majority of treatment-emergent symptomatic overall ARIA-H was mild to moderate, with few LEC10-BW subjects reporting severe symptomatic ARIA-H. Of the 2/1616 (0.1%) severe overall ARIA-H reported in the Overall Population, both occurred in homozygous *APOE4* carriers and were concurrent with ARIA-E (Table 76) (Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.25.1a, Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.1, and Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.5).

Table 76. Severity of symptomatic ARIA-H (isolated and overall) – study 301 OLE – LEC10-BW-treated period (safety analysis set)

	Lecanemab 10 mg/kg Biweekly		
	Clinical Severity n/m (%)		
Population (n, %)	**Mild**	**Moderate**	**Severe**
Overall ARIA-H			
Overall	20/1616 (1.2)	11/1616 (0.7)	2/1616 (0.1)
Noncarrier and Heterozygous *APOE4* Carriers	12/1366 (0.9)	7/1366 (0.5)	0
Individual Genotype			
Noncarriers	3/497 (0.6)	2/497 (0.4)	0
Heterozygous *APOE4* Carriers	9/869 (1.0)	5/869 (0.6)	0
Homozygous *APOE4* Carriers	8/250 (3.2)	4/250 (1.6)	2/250 (0.8)
Isolated ARIA-H			
Overall	5/1616 (0.3)	3/1616 (0.2)	0
Noncarrier and Heterozygous *APOE4* Carriers	4/1366 (0.3)	3/1366 (0.2)	0
Individual Genotype			
Noncarriers	1/497 (0.2)	1/497 (0.2)	0
Heterozygous *APOE4* Carriers	3/869 (0.3)	2/869 (0.2)	0
Homozygous *APOE4* Carriers	1/250 (0.4)	0	0

APOE4 = apolipoprotein E4 variant, ARIA-H = amyloid-related imaging abnormality-haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category, n = number of subjects with an event in each category, OLE = open-label extension.
Source: Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.26a, Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.1, and Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.5.

In the LEC10-BW-treated set, in the Overall Population 2 subjects with severe treatment-emergent ARIA-H symptoms reported the following symptoms (Appendix 1 Study 301 OLE sCSR5 Listing 16.2.7.5):

- Seizure, dysarthria, hemiplegia: 1 subject (Subject; homozygous *APOE4* carrier)
- Headache: 1 subject (Subject; homozygous *APOE4* carrier)

Postmarketing Experience (Up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

There have been 26 symptomatic events of ARIA-H (microhaemorrhage or superficial siderosis).

Consistent with the description of symptomatic ARIA in the proposed product information, symptoms were generally mild to moderate with the most commonly reported symptoms being headache and confusion. Additional symptoms associated with ARIA-H included vision changes, dizziness/balance issues, memory loss, and tiredness, although more severe symptoms including seizures have also been reported.

The majority of reports of symptomatic ARIA-H were concurrent with ARIA-E (81%). Radiographic severity was mild in 3 events, moderate in 2 events, and severe in 4 events. For the remaining events, radiographic severity was not known. There were 2 reports of symptomatic ARIA-H in noncarriers, 5 in heterozygous *APOE4* carriers, and 3 in homozygous *APOE4* carriers. For the remaining events, *APOE4* status was not known. There was 1 report of symptomatic ARIA-H in which the patient was receiving concomitant aspirin and no reports of symptomatic ARIA-H in which the patient was concomitantly taking an anticoagulant or had received a thrombolytic.

While the number of patients treated commercially with lecanemab is not known and a reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, the rate of serious ARIA-H (based on an estimated reporting rate of 0.008 per patient-year of exposure) is consistent with that observed in the clinical development programme.

The incidence of symptomatic ARIA-H (microhaemorrhage and superficial siderosis) in the Japanese postmarketing data was 0.04%. Of note, *APOE4* genotype data is limited due to access to *APOE4* testing in Japan.

All reports of symptomatic ARIA-H (cerebral microhaemorrhage and superficial siderosis) were concurrent with ARIA-E. There were no reports of symptomatic ARIA-H in which the patient was receiving a concomitant antiplatelet, anticoagulant or had received a thrombolytic.

5.1.1.3.5. Proposed Risk Minimisation Measures and Additional Pharmacovigilance for ARIA-E and ARIA-H

ARIA events are detectable, and the applicant has proposed a number of activities to support HCPs in the monitoring for these events and to ensure HCPs are aware of appropriate patient management if these events occur. This patient management includes both radiographic and symptomatic events. Further details on the HCP Guide and Checklist, as well as the Patient Alert Card, are provided in Annex 6 of the risk management plan (RMP).

A follow up questionnaire to be used by HCPs when reporting postmarketing ARIA-E, -H and ICH>1 cm events is proposed to support the characterisation of these events, with this data to be reported in PSURs.

A PASS to further characterize ARIA-E, -H and ICH>1 cm, effectiveness of RMMs, and drug utilisation is also proposed. An outline is provided in Section 5.1.1.3.13. .

A comprehensive tabular summary outline of all risk minimisation measures and additional pharmacovigilance activities is provided in Table 88.

Routine Risk Communication

- SmPC Section 4.2
  - Treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease in centres with timely access to MRI.
  - Obtain a recent (within 6 months) baseline brain MRI prior to initiating treatment with lecanemab to evaluate for pre-existing ARIA.
  - Obtain an MRI prior to the 5th, 7th, and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed including an MRI.
  - Requires suspension of dosing for any symptomatic or radiographically moderate or severe ARIA-E and -H.
  - A follow-up MRI to assess for resolution/stabilization 2 to 4 months after initial identification should be performed.
  - Once the MRI demonstrates radiographic resolution/stabilization and symptoms, if present, resolve, resumption of dosing should be guided by clinical judgment.
  - After the second occurrence of symptomatic or radiographically moderate or severe ARIA-E, treatment with lecanemab should be discontinued.
  - After the second occurrence of severe ARIA-H, treatment with lecanemab should be discontinued.
- SmPC Section 4.3

- Contraindication for patients with MRI findings suggestive of severe CAA, defined as >4 microhaemorrhages or an area of superficial siderosis on pre-treatment MRI.

- SmPC Section 4.4
  - Symptoms associated with ARIA are described, highlighting that serious and life-threatening events, including seizure as a symptom of ARIA, rarely can occur.
  - Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Leqembi.
  - Risk of ARIA is increased in *APOE4* homozygote carriers.
  - Recommendation to consider the benefit of lecanemab for the treatment of AD and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment.
  - Recommends periodic monitoring with MRI.
  - Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with lecanemab.
  - If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including additional MRI testing.

Healthcare Professional Guide and Checklist

The guide reinforces the need for enhanced clinical vigilance during the first 14 weeks of treatment for ARIA. Where a patient experiences a symptom, HCPs are recommended to undertake clinical evaluation, including MRI. Recommendations for dosing interruptions, in line with the SmPC are reiterated.

Patient Alert Card

The Patient Alert Card focuses on providing targeted information on the potential clinical symptoms in the setting of ARIA and to reinforce the importance of seeking medical advice in a timely manner, thus promoting patient safety.

Follow-Up Questionnaire

To monitor the nature of reports of suspected ARIA in postmarketing, an ARIA specific questionnaire has been developed to further characterise the risk.

ARIA Education

The Applicant will be working with the European AD specialists and neuroradiologists to increase ARIA awareness and provide educational materials (Section 0)

5.1.1.3.6. Seizures, Including Those Associated With ARIA-E or -H

The risk of seizures is elevated in AD and seizures have also been reported as a symptom of severe ARIA-E and -H (Irizarry, et al., 2012).

In Study 301 Core, cases of treatment-emergent seizure not associated with ARIA were similar on PBO and LEC10-BW. Cases of seizure concurrent with ARIA were rare, with 1/897 (0.1%) on PBO and 3/898 (0.3%) on LEC10-BW. All 3 LEC10-BW subjects' ARIA resolved radiographically and clinically, one with sequelae of partial seizures with secondary generalisation who received anti-convulsive medication, levetiracetam, for seizure prophylaxis. One patient in the OLE Phase died after severe ARIA-E and -H that presented with seizures.

The seizure summary that follows does not contain new analyses, although a new tabulated summary of baseline characteristics is provided to facilitate your review.

Incidence of Seizure Without and With ARIA-E or -H Events

Study 301 Core (18 Months Placebo-Controlled Treatment)

In Study 301 Core, treatment-emergent cases of seizure not associated with ARIA-E or ARIA-H was 3/897 (0.3%) for PBO and 2/898 (0.2%) for LEC10-BW.

Treatment-emergent seizure concurrent with ARIA rarely occurred, with 1/897 (0.1%) for PBO and 3/898 (0.3%) for LEC10-BW (Table 77).

Table 77. Incidence of treatment-emergent seizure associated and not associated with ARIA-E or ARIA-H – study 301 core (safety analysis set)

	Placebo N = 897	**Lecanemab 10 mg/kg Biweekly N = 898**
Seizure Overall	4/897 (0.4)	5/898 (0.6)
Seizure Not Associated With ARIA-E and/or -H	3/897 (0.3)	2/898 (0.2)
Exposure-adjusted rate (per patient-year)	0.0024	0.0017
Seizure With Concurrent ARIA and/or -H	1/897 (0.1)	3/898 (0.3)
Exposure-adjusted rate (per patient-year)	0.0008	0.0025

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage.
Source: Study 301 Core Table 14.3.1.1.1, Listing 16.2.7.1, and Listing 16.2.7.5.

Table 78 presents all treatment-emergent subjects with events and symptoms in the Standardised MedDRA Query of seizure organised by concurrence with ARIA (-E, -H). Baseline characteristics including *APOE4* genotype, sex, age, race, clinical subgroup, and use of concomitant AD medication were explored in subjects who experienced seizure with or without ARIA. Characteristics were well balanced for both the PBO and LEC10-BW subjects with seizure.

Abbreviated narratives are provided below:

- A noncarrier patient who received PBO in the Core. On Day 175, the subject was found on the floor, attributed to a fall, syncopal episode, and seizure, resulting in hospitalisation. A CT scan and CT angiogram showed acute subarachnoid haemorrhage in the right posterior frontal, right parietal, and left frontoparietal junctions; no intracranial aneurysm or cerebral oedema was noted. MRI showed ARIA-H (superficial siderosis) in the right frontal (40 mm), right parietal (40 mm), and left frontal (15 mm) regions and radiographically moderate ARIA-E. Treatment with study drug was permanently discontinued. The subject was discharged from the hospital on Day 178. ARIA-E resolved radiographically on Day 272.

  On Day 209, the subject had a syncope episode, fell, and was found on the floor with large scalp bruising. A CT of the head showed post-traumatic subarachnoid haemorrhage in the right parietal lobe. The subject was treated with levetiracetam for 3 days and valproic acid which was ongoing. On Day 211, a repeat CT of the head showed that the subarachnoid hematoma was resolved.

- A homozygous *APOE4* patient who received LEC10-BW in the Core. An adverse event of ARIA-H was reported on Day 192 with 1 new microhaemorrhage on study MRI. The subject was asymptomatic. On Day 213, the subject developed fever and experienced 2 possible seizures and

syncope, resulting in hospitalisation. The subject was diagnosed with acute diverticulitis and COVID-19. The subject was treated with levetiracetam 250 mg PO BID for 6 weeks for the event of seizure. The subject continued on study drug. It is noted that since the subject's event of ARIA-H microhaemorrhage did not resolve radiographically, the event of seizure overlapped with the ongoing ARIA-H but was not considered a symptom of the ARIA-H.

- heterozygous *APOE4* patient who received LEC10-BW in the Core. The subject was on anticoagulation (rivaroxaban for prior DVT/PE). On Day 156, the subject had difficulty walking and on arrival at the emergency room (ER) had a convulsive seizure with post-ictal hemianopsia, aphasia and confusion, followed by a secondarily generalised tonic-clonic seizure. Hospital MRI showed vasogenic oedema in left parieto-occipital-temporal and right occipital-temporal regions, which was reported as severe, symptomatic ARIA-E. The electroencephalogram (EEG) was consistent with metabolic encephalopathy. The subject was hospitalised, and the hospital course was complicated by pulmonary oedema and transient atrial fibrillation. The patient was maintained on lacosamide, with no further seizures. The subject was permanently discontinued from study drug. MRI on Day 213 showed radiographic resolution of ARIA-E.

- A homozygous *APOE4* patient who received LEC10-BW in the Core. On Day 47, an adverse event of radiographically severe ARIA-E was reported. The event of ARIA-E required hospitalisation, as it was symptomatic, with mild blurry vision that began on the same day (Day 35) which was mild in severity and resolved on Day 85 and with focal to bilateral tonic-clonic seizure on Day 52, which resolved on Day 54. The event of ARIA-E was reported as severe in clinical severity, serious (hospitalisation), and deemed related to study drug.

All events of ARIA-E resolved radiographically and clinically, with the seizure resolving shortly after the radiographic identification of the ARIA-E. There was one subject with sequelae of partial seizures with secondary generalisation who received ongoing anti-convulsive medication, levetiracetam, for seizure prophylaxis.

Table 78. Baseline characteristics for subjects with seizure (without and with concurrent ARIA-E or -H) – study 301 core (safety analysis set)

Subject ID	Treatment	Association Radiographic Severity	*APOE4* Status	Sex	Age[a]	Stage	AD Med
Without concurrent ARIA-E or ARIA-H							
	PBO	-	Noncarrier	M	60	MCI	No
	PBO	-	Noncarrier	M	70	MCI	Yes
	PBO	-	Homozygous *APOE4* Carrier	M	66	MCI	No
	LEC10-BW	-	Noncarrier	F	82	Mild AD	Yes
	LEC10-BW	-	Homozygous *APOE4* Carrier	F	59	MCI	No
With concurrent ARIA-E and or ARIA-H							
	PBO	ARIA-E/H severity: moderate (ARIA-E), severe (ARIA-H SS)	Noncarrier	F	71	Mild AD	No
	LEC10-BW	ARIA-H microhem severity: mild	Homozygous *APOE4* Carrier	F	73	Mild AD	Y
	LEC10-BW	ARIA-E severity: severe	Homozygous *APOE4* Carrier	M	68	MCI	No
	LEC10-BW	ARIA-E severity: missing	Heterozygous *APOE4* Carrier	F	68	MCI	No

AD = Alzheimer's disease, *APOE4* = apolipoprotein E4 variant, ARIA = amyloid-related imaging abnormality, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, BMI = body mass index, F = female, LEC10-BW = lecanemab 10 mg/kg biweekly, M = male, MCI = mild cognitive impairment, Med = medication, PBO = placebo, SS = superficial siderosis.

Table 78. Baseline characteristics for subjects with seizure (without and with concurrent ARIA-E or -H) – study 301 core (safety analysis set)

a: Age is age at onset of ARIA event.
Source: Study 301 Core Listing 16.2.7.1 and Listing 16.2.7.5.

Study 301 OLE Phase (36 Months Total Treatment)

In the LEC10-BW Treated Period, there were 15/1616 (0.9%) subjects with treatment-emergent seizure not associated with ARIA-E or ARIA-H (Table 79). Cases of treatment-emergent seizure concurrent with ARIA-E or ARIA-H were infrequent, 11/1616 (0.7%) subjects. This count includes the 5 subjects treated with LEC10-BW in the Core.

Table 79. Incidence of seizure associated and not associated with ARIA-E or ARIA-H – study 301 OLE – LEC10-BW-treated period (safety analysis set)

	Lecanemab 10 mg/kg Biweekly N = 1616
Seizure Overall	26/1616 (1.6)
Seizure Not Associated With ARIA	15/1616 (0.9)
Exposure-adjusted rate (per patient-year)	0.0043
Seizure With Concurrent ARIA	11/1616 (0.7)
Exposure-adjusted rate (per patient-year)	0.0032

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, OLE = open-label extension.
Source: Study 301 OLE sCSR5 Table 14.3.1.1.5, Listings 16.2.7.1, and 16.2.7.5.

Abbreviated narratives are provided below:

- Subject heterozygous *APOE4* [redacted], who received PBO in the Core then LEC10-BW in the OLE Phase. On Extension Day 57 the subject fell resulting in a C6 cervical vertebral fracture. MRI showed severe ARIA-E in bilateral frontal, temporal, and parietal regions and right occipital region and severe ARIA-H with >10 new microhaemorrhages. Upon examination, the neurologist indicated that the subject may have experienced a seizure before the fall. The subject was treated with levetiracetam 500 mg BID and a course of Decadron for ARIA-E. EEG on Day 58 showed mild diffuse slowing with asymmetric left hemispheric slowing. The study treatment was discontinued. ARIA-E was ongoing radiographically and decreased in size on MRI on Day 103.
- Subject [redacted]: See narrative below.
- Subject [redacted]: [redacted] noncarrier [redacted] who received LEC10-BW in the Core and continued to receive LEC10-BW in the OLE Phase. On Day 578 the subject had an event of epilepsy and initiated levetiracetam. On Day 917, MRI showed ARIA-H with one new microhaemorrhage. Since the event of epilepsy was ongoing at the time of the microhaemorrhage, these were considered concurrent, but there is no indication these two events were related to one another.
- Subject [redacted]: heterozygous *APOE4* [redacted] who received PBO in the Core then received LEC10-BW in the OLE Phase. On Extension Day 30, the subject complained of headache. On Day 31, the subject was taken to the ER for disorientation. In the ER, the subject was noted with left

sided gaze deviation, blood in the mouth, and weakness, and it was suggested that the subject had possibly experienced a seizure. MRI showed severe ARIA-E in bilateral frontal, temporal, and occipital lobes and right parietal lobe with 2 new microhaemorrhages. The subject was treated with levetiracetam (ongoing) and a course of dexamethasone for ARIA-E. The study drug was permanently discontinued.

- Subject [redacted] heterozygous *APOE4* [redacted] who received PBO in the Core then received LEC10-BW in the OLE Phase. On Extension Day 92, MRI showed mild radiographic ARIA-E in the left parietal and occipital lobes and 2 new microhaemorrhages. The subject received a subsequent dose of LEC10-BW on Day 106. On Day 107, the subject became confused and dysphasic and was hospitalised with symptomatic ARIA-E. That evening, the subject had a generalised seizure, treated with sodium valproate. Corticosteroid treatment was initiated for ARIA-E. EEG showed epileptiform activity, which had resolved on EEG on Day 127. ARIA-E resolved on Day 162. The study drug was permanently discontinued.

- Subject [redacted] homozygous *APOE4* [redacted] who received LEC10-BW in the Core continued to receive LEC-10BW in the OLE Phase. On Day 589 (Extension Day 41), the subject experienced two generalised tonic-clonic seizures and was admitted to the neurology department. MRI showed severe ARIA-E in right frontal, bilateral temporal, parietal and occipital lobes, with 53 new microhaemorrhages. The subject received a course of methylprednisolone for ARIA-E, while being maintained on levetiracetam. The subject had no further seizures, and ARIA-E resolved radiographically on Day 696 (Extension Day 148). The study drug was permanently discontinued.

- Subject [redacted] patient homozygous *APOE4* carrier who received PBO in the Core then received LEC10-BW in the OLE. On Extension Day 28 the study MRI showed radiographically severe ARIA-E in the right frontal, right temporal (nonhippocampal), right parietal, bilateral occipital and bilateral cerebellum regions with 61 new microhaemorrhages. The subject developed symptoms of headache on Day 41, homonymous hemianopia on Day 49 and confusion, visual difficulties, gait disturbance and focal onset impaired awareness seizure on Day 50 resulting in hospitalisation. EEG showed periodic lateralised epileptiform discharges. Subject was treated with a course of corticosteroids for ARIA-E and clobazam (for 2 months) and lacosamide (ongoing) for seizure. ARIA-E resolved radiographically on Day 191. Study drug was permanently discontinued.

- A [redacted] heterozygous *APOE4* patient who received PBO in the Core then received LEC10BW in the OLE Phase. On Extension Day 27, the subject had 3 seizures lasting 1-3 minutes with left gaze, altered mental status, and left-hand tremor. In the ER, the patient had post-ictal left gaze preference and left arm weakness and was hospitalised. MRI showed ARIA-E in bilateral parieto-occipital and temporal lobes, with superficial siderosis. Study drug was permanently discontinued. The subject was treated with levetiracetam and corticosteroids, with no further seizures. The event of ARIA-E resolved on Day 306.

Postmarketing Experience (Up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

There have been 15 reports of seizures with 7 coinciding with ARIA events. The risk for seizures in association with ARIA is described in the proposed product information and is discussed further below. Considering the known risk for seizures in patients with AD (as illustrated by the PBO rate in Study 301 of 0.3%, which was the same rate for patients treated with LEC10-BW not associated with ARIA), the rate of seizures appears to be consistent with that observed clinical development programme and the population being treated.

There have been 7 reports of seizures in patients who have experienced ARIA-E events, including 4 reports with concurrent ARIA-H. There were no reports in patients with isolated ARIA-H. Two reports are discussed in Section 5.1.1.3.8. . A summary of the remaining reports is provided below:

- This spontaneous physician report describes a [redacted], *APOE4* status unknown, who had a grand mal seizure 2 days after the third infusion of lecanemab and was taken to the ER where the patient was diagnosed with ARIA-E and ARIA-H. Lecanemab was permanently discontinued. The patient was not hospitalised. The outcome of the event, treatment provided, action taken with lecanemab, past medical history and concomitant medications were not known.

- This spontaneous physician report describes a patient who was hospitalised with seizures following the sixth infusion of lecanemab. The physician reviewed the MRI from prior to the fifth infusion, which had been reported as "okay" by the radiologist and the physician suspected the MRI showed ARIA. The outcome of the event, treatment provided, action taken with lecanemab, past medical history and concomitant medications were not known.

- This spontaneous healthcare professional report describes a [redacted] *APOE4* heterozygous patient who was hospitalised with a seizure following the third infusion of lecanemab and was treated with levetiracetam. An MRI revealed ARIA-E in the left occipital lobe. Lecanemab was interrupted. Seizures resolved and the patient was discharged. On a repeat MRI the patient was noted to have worsening ARIA-E and new ARIA-H without recurrence of seizures and the ARIA-E subsequently resolved and the ARIA-H stabilised (reported as not recovered). The patient did not have any history of seizures.

- This spontaneous physician report describes a [redacted], *APOE4* status unknown, who was developed a migraine approximately 6 weeks after starting lecanemab. The patient then received their fourth infusion. [redacted] The patient was diagnosed with ARIA-E on the first monitoring MRI. Lecanemab was interrupted. The patient was then hospitalised with a seizure and lecanemab was permanently discontinued. The patient recovered from the ARIA-E and seizures and the migraine improved. Past medical history and concomitant medications were not known.

- Spontaneous physician report describes a [redacted] patient, *APOE4* status unknown, who experienced ARIA (described as hippocampal) and seizure an unknown latency after starting lecanemab. The action taken with lecanemab was not known. The patient had a second episode of ARIA (location not provided) and seizure. The outcome of the event, treatment provided, action taken with lecanemab, past medical history and concomitant medications were not known.

While the number of patients treated commercially with lecanemab is not known and a reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, the rate of ARIA-E with symptoms of seizures (based on an estimated reporting rate of 0.0025 per patient-year of exposure) is consistent with that observed in the clinical development programme.

There was 1 report of seizure in association with ARIA-E in the Japanese postmarketing setting which is described below:

- This report describes [redacted], *APOE4* status unknown who was hospitalised with status epilepticus an unknown latency after starting lecanemab and was diagnosed with ARIA-E on MRI. Additional symptoms included headache, chills, nausea and consciousness disturbed. Lecanemab was discontinued and the patient was treated with unspecified anti-epileptics for seizure prophylaxis. The patient recovered from the events. Past medical history and concomitant medications were not known.

5.1.1.3.7. Intracerebral Haemorrhage >1 cm in Diameter

ICH>1 cm in the lobar brain regions can occur spontaneously in AD in the absence of anti-amyloid therapies and can cause focal neurological symptoms (ICH>1 cm in the deep brain regions or brain stem is usually related to hypertension). The pathophysiology is vascular amyloid deposition leading to loss of the vascular smooth muscle layer, friability of blood vessels, and haemorrhage (Koemans, et al., 2023). In AD clinical trials, the rate of ICH>1 cm in PBO ranges from 0.4% – 1% and a meta-analysis of observational studies found rates of ICH>1 cm in AD of 2.7 - 5.2 per 1000 person-years (Waziry, et al., 2020).

Risk factors for ICH>1 cm in the absence of anti-amyloid therapies are CAA, *APOE4* genotype, anticoagulants, and thrombolytics. Patients were excluded from enrolment in Study 301 for findings on neuroimaging that indicated an increased risk for ICH>1 cm. These included findings suggestive of severe CAA (prior cerebral haemorrhage >1 cm in diameter, more than 4 microhaemorrhages, superficial siderosis, vasogenic oedema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of ICH>1 cm in diameter.

The incidence of ICH>1 cm with LEC10-BW was low, 6/898 (0.7%, 0.0051 per patient-year of exposure) (vs 2/897 [0.2%] PBO, 0.0016 per patient-year of exposure) in the Overall Population (note: the values for ICH>1 cm reflect all reported cases, not only those defined as treatment-emergent). Although there were few events reported, which limits the ability to draw conclusions, of the genotypes, homozygous *APOE4* carriers had a higher incidence of ICH>1 cm. When homozygous *APOE4* carriers are removed from the analyses (Noncarrier and Heterozygous *APOE4* Carrier Population) the incidence was 2/764 (0.3%) subjects on PBO (0.0019 per patient-year of exposure) and 4/757 (0.5%) subjects on LEC10-BW (0.0040 per patient-year of exposure).

In the OLE Phase ("LEC10-BW Treated Period" which represents all patients treated with LEC10-BW in the Core and OLE Phase) in the Noncarrier and Heterozygous *APOE4* Carrier Population the incidence was 8/1366 (0.6%) (0.0027 per patient-year of exposure).

Across both the Core and OLE Phase, ICH>1 cm occurred throughout the treatment period, with symptoms including dysarthria, hemiparesis, asthenia, headache, and speech disorder. There was 1 subject (noncarrier) on PBO in the Core with isolated ICH>1 cm with a fatal outcome, and 2 deaths with concurrent ICH>1 cm on LEC10-BW in the OLE Phase (1 noncarrier with subacute ICH>1 cm, and 1 homozygous *APOE4* carrier with multiple ICH>1 cm after tPA).

Available postmarketing experience (up to 18 months) indicates that the rate of ICH>1 cm reported appears to be consistent with that observed clinical development programme and the population being treated. Unlike prior sections where postmarketing data are provided by incidence, severity, seriousness and symptomatic, given the few events, postmarketing data for ICH>1 cm are provided in a single summary section below.

In response to CHMP questions, the applicant evaluated concomitant anticoagulant and/or antiplatelet use and the risk of ICH>1 cm. Subjects on LEC10-BW with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of ICH>1 cm of 2.6% (2/78) compared to no PBO subjects. The small number of events limits definitive conclusions on the risk associated with concomitant anticoagulant medication.

ICH>1 cm events are rare. The proposed SmPC indication excludes homozygous *APOE4* carriers and provides and contraindicates treatment in subjects with findings suggestive of severe CAA. A summary paragraph on ICH>1 cm rates reported in Study 301 has also been added by the applicant as part of this re-examination procedure. There is also a requirement for permanent discontinuation of lecanemab after the first ICH>1 cm event. Precautionary language is provided regarding administration of thrombolytic agents and anticoagulants.

The Applicant has proposed a number of activities to support HCPs in the monitoring for these events and to ensure HCPs are aware of appropriate patient management if these events occur. Pharmacovigilance activities including a follow up questionnaire to be used by HCPs when reporting postmarketing ICH>1 cm events as well as a PASS to further characterise ARIA-E, -H and ICH>1 cm, effectiveness of RMMs and drug utilisation are also planned.

The ICH>1 cm summary that follows contains both previously submitted and new analyses.

(1) Incidence and Severity for ICH>1 cm in Diameter

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

In Study 301 Core, the incidence of ICH>1 cm (treatment-emergent and non-treatment-emergent) was lower in PBO than LEC10-BW (Table 80). There were few events reported which limits the ability to draw conclusion, however, of the genotypes, homozygous *APOE4* carriers had a higher incidence of ICH>1 cm 2/141 (1.4%), compared to noncarriers 1/278 (0.4%) and heterozygous *APOE4* carriers 3/479 (0.6%).

Table 80. Incidence of intracerebral haemorrhage >1 cm – study 301 core (safety analysis set)

Population	**Placebo n/m (%)**	**Lecanemab 10 mg/kg Biweekly n/m (%)**
Overall	2/897 (0.2)	6/898 (0.7)
Noncarrier and Heterozygous *APOE4* Carrier	2/764 (0.3)	4/757 (0.5)
Individual Genotype		
Noncarriers	1/286 (0.3)	1/278 (0.4)
Heterozygous *APOE4*	1/478 (0.2)	3/479 (0.6)
Homozygous *APOE4*	0/133 (0)	2/141 (1.4)

APOE4 = apolipoprotein E4 variant, m = number of subjects in each category, n = number of subjects with an event in each category.
Table includes 2 subjects (1 PBO, 1 LEC10-BW) with events that were not treatment-emergent.
Source: Study 301 Core CSR Table 14.3.2.6.10.4.

ICH>1 cm are distributed throughout the treatment period for both PBO and LEC10-BW in the Core (Study 301 Core CSR Listing 16.2.7.1). Clinically severe ICH>1 cm was reported in 1 PBO subject. For LEC10-BW, events were mostly mild or moderate in clinical severity (2 subjects each) with 2 severe ICH>1 cm reported (Table 81). All cases of ICH>1 cm were ongoing radiographically at the time of reporting of Study 301 Core, which is expected (Study 301 Core CSR Table 14.3.2.6.38), with the exception of the 1 fatal case on PBO.

Table 81. Clinical severity of intracerebral haemorrhage >1 cm – study 301 core (safety analysis set)

Population	Placebo n/m (%)			Lecanemab 10 mg/kg Biweekly n/m (%)		
	Clinical Severity			Clinical Severity		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Overall	0	1/897 (0.1)	1/897 (0.1)	2/898 (0.2)	2/898 (0.2)	2/898 (0.2)
Noncarrier and Heterozygous *APOE4* Carriers	0	1/764 (0.1)	1/764 (0.1)	1/757 (0.1)	1/757 (0.1)	2/757 (0.3)
Individual Genotype						
Noncarriers[a]	0	0	1/286 (0.3)	0	1/278 (0.4)	0
Heterozygous *APOE4* Carriers[b]	0	1/478 (0.2)	0	1/479 (0.2)	0	2/479 (0.4)
Homozygous *APOE4* Carriers[c]	0	0	0	1/141 (0.7)	1/141 (0.7)	0

APOE4 = apolipoprotein E4 variant, m = number of subjects in each category, n = number of subjects with an event in each category.
Table includes 2 subjects (1 PBO with moderate severity, 1 LEC10-BW with severe severity) with events that were not treatment-emergent.
a: Among all noncarriers in the lecanemab group with ICH>1 cm (n=2), the distribution was 1/2 (50.0%) moderate and 1/2 (50.0%) severe.
b: Among all heterozygous *APOE4* carriers in the lecanemab group with ICH>1 cm (n=2), the distribution was 1/2 (50.0%) mild and 1/2 (50.0%) was severe.
c: Among all homozygous *APOE4* carriers in the lecanemab group with ICH>1 cm (n=2), the distribution was 1/2 (50.0%) mild and 1/2 (50.0%) was moderate.
Source: Study 301 Core CSR Table 14.3.2.6.10.2.

Study 301 Open Label Extension (36 Months Total Treatment)

Data presented for Study 301 OLE Phase are cumulative for any subject who received at least 1 dose of LEC10-BW at any time, whether in the Core Study or OLE Phase (31 Mar 2024) (i.e., LEC10-BW Treated Period). Therefore, these data are a pooled presentation of all LEC10-BW treated subjects across the total duration of Study 301. Data presented for the OLE Phase reflect up to 36 months treatment with LEC10-BW.

In the LEC10-BW-Treated Period, the incidence of ICH>1 cm in the Overall Population was 11/1616 (0.7%) subjects (Table 82). Again, there were few events reported which limits the ability to draw conclusion, however, of the genotypes, homozygous *APOE4* carriers had a higher incidence of ICH>1 cm (3/250 [1.2%]) compared to noncarriers (2/497 [0.4%]) and heterozygous *APOE4* carriers (6/869 [0.7%]). In the Noncarrier and Heterozygous *APOE4* Carrier Population the incidence was 8/1366 (0.6%).

Table 82. Incidence of intracerebral haemorrhage >1 cm – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	Lecanemab 10 mg/kg Biweekly n/m (%)
Overall	11/1616 (0.7)
Noncarrier and Heterozygous *APOE4* Carriers	8/1366 (0.6)
Individual Genotype	
Noncarriers	2/497 (0.4)
Heterozygous *APOE4* Carriers	6/869 (0.7)
Homozygous *APOE4* Carriers	3/250 (1.2)

APOE4 = apolipoprotein E4 variant, LEC10-BW = lecanemab 10 mg/kg biweekly, m = number of subjects in each category, n = number of subjects with an event in each category, OLE = open-label extension.
Table includes 1 subject (1 LEC10-BW) with events that were not treatment-emergent.
Source: Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.1a.

Similar to the Core, ICH>1 cm occurred throughout the OLE Phase. Events were mostly mild (6 subjects) in clinical severity. Moderate ICH>1 cm were reported in 2 subjects and severe ICH>1 cm in

3 subjects (Table 83). Events of ICH>1 cm resolved in 1 subject, were fatal in 2 subjects on LEC10-BW, and are ongoing in 8 subjects. Fatal events are described in Section 5.1.1.3.8.

Table 83. Clinical severity of intracerebral haemorrhage >1 cm – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Population	**Lecanemab 10 mg/kg Biweekly n/m (%)**		
	Clinical Severity		
	Mild	**Moderate**	**Severe**
Overall	6/1616 (0.4)	2/1616 (0.1)	3/1616 (0.2)
Noncarrier and Heterozygous *APOE4* Carriers	5/1366 (0.4)	1/1366 (0.1)	2/1366 (0.1)
Individual Genotype			
Noncarriers[a]	1/497 (0.2)	1/497 (0.2)	0
Heterozygous *APOE4* Carriers[b]	4/869 (0.5)	0	2/869 (0.2)
Homozygous *APOE4* Carriers[c]	1/250 (0.4)	1/250 (0.4)	1/250 (0.4)

APOE4 = apolipoprotein E4 variant, m = number of subjects in each category, n = number of subjects with an event in each category.
Table includes 1 subject (1 LEC10-BW) with events that were not treatment-emergent.
a: Among all noncarriers in the lecanemab group with ICH>1 cm (n=2), the distribution was 1/2 (50.0%) mild and 1/2 (50.0%) moderate.
b: Among all heterozygous *APOE4* carriers in the lecanemab group with ICH>1 cm (n=6), the distribution was 4/6 (66.7%) mild and 2/6 (33.3%) severe.
c: Among all homozygous *APOE4* carriers in the lecanemab group with ICH>1 cm (n=3), the distribution was 1/3 (33.3%) mild, 1/3 (33.3%) moderate, and 1/3 (33.3%) severe.
Appendix 1 sCSR5 Table 14.3.2.6.10.2a.

(2) Serious Adverse Events due to ICH>1 cm in Diameter

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

There were 2 subjects with serious ICH>1 cm in PBO, and 4 in LEC10-BW (Table 84). For LEC10-BW, of the genotypes in LEC10-BW, homozygous *APOE4* carriers had a higher incidence of serious ICH>1 cm in diameter (1/141 [0.7%]) compared to noncarriers (1/278 [0.4%]) and heterozygous *APOE4* carriers (2/479 [0.4%]).

Table 84. Serious adverse events of and intracerebral haemorrhage >1 cm in diameter – study 301 core (safety analysis set)

Subject Identifier	Preferred Term or Subcategory	Isolated ARIA-H or Concurrent with ARIA-E	Genotype	Core Treatment Group
	Cerebral haemorrhage	Concurrent	Homozygous	LEC10-BW
	Cerebral haemorrhage	Isolated	Heterozygous	LEC10-BW
	Cerebral haemorrhage	Isolated	Noncarrier	PBO
	Cerebral haemorrhage	Isolated	Noncarrier	LEC10-BW
Not Treatment Emergent				
	Cerebral haemorrhage	Concurrent	Heterozygous	PBO
	Cerebral haemorrhage	Concurrent	Heterozygous	LEC10-BW

Concurrent is defined as overlapping in the AE duration of 2 ARIA events.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.
Source: Study 301 Core CSR Listing 16.2.7.1.

Study 301 OLE (36 Months Total Treatment)

In the LEC10-BW-Treated Period, the incidence of serious ICH>1 cm was low (Table 85). The few events limit the ability to draw conclusions by genotype: homozygous *APOE4* carriers was 2/250 (0.8%) compared to noncarriers (2/497 [0.4%]) and heterozygous *APOE4* carriers (3/869 [0.3%]).

Table 85. Serious adverse events of and intracerebral haemorrhage >1 cm in diameter – study 301 OLE – LEC10-BW-treated period (safety analysis set)

Subject Identifier	Preferred Term or Subcategory	Isolated ARIA-H or Concurrent with ARIA-E	Genotype
LEC10-BW Treated Period			
	Cerebral haemorrhage	Concurrent	Homozygous
	Cerebral haemorrhage	Concurrent	Heterozygous
	Cerebral haemorrhage	Concurrent	Noncarrier
	Cerebral haemorrhage	Isolated	Heterozygous
	Cerebral haemorrhage	Isolated	Homozygous
	Cerebral haemorrhage	Concurrent	Heterozygous
	Cerebral haemorrhage	Isolated	Noncarrier

Concurrent is defined as overlapping in the AE duration of 2 ARIA events.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality-haemorrhage, LEC10-BW = lecanemab 10 mg/kg biweekly.
Table includes 1 subject with events that were not treatment emergent.
Source: Appendix 1 Study 301 OLE sCSR 5 Listing 16.2.7.1, Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.2.3, and Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.1.2.

(3) Symptomatic ICH >1cm in Diameter

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

In Study 301 Core, 3 (0.3%) LEC10-BW subjects had symptomatic ICH>1 cm that were moderate to severe in clinical severity (Study 301 Core CSR Table 14.3.2.6.26, Listing 16.2.7.1). Symptoms reported were (Study 301 Core CSR Table 14.3.2.6.27.2, Listing 16.2.7.5):

- Dysarthria, hemiparesis, asthenia (ongoing at the time or reporting on Study 301 Core) reported in 1 (0.1%) subject (heterozygous *APOE4* carrier)
- Speech disorder and behavior disorder (all resolved) reported in 1 (0.1%) subject (noncarrier)

- Headache, monoparesis, partial seizures (all resolved) reported in 1 (0.1%) subject (heterozygous *APOE4* carrier)

Study 301 OLE (36 Months Total Treatment)

Three subjects (0.2%) had symptomatic ICH>1 cm with LEC10-BW (note: the values for ICH>1 cm reflect all reported cases, not only those defined as treatment-emergent) (Appendix 1 sCSR5 Table 14.3.2.6.26a). There were no new symptomatic ICH>1 cm in the OLE Phase; these are the same subjects described in Section 0.

Postmarketing Experience (Up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

The following PTs were used for ICH: cerebral haematoma, cerebral haemorrhage, haemorrhage intracranial, haemorrhagic cerebral infarction, haemorrhagic stroke, and intraventricular haemorrhage.

There have been 12 events of ICH. The size of the haemorrhage was not available for any of the reports.

Five reports were consumer or office staff reports received via specialty pharmacies with a verbatim term of brain bleed or brain bleeding for which additional information was not available despite follow up attempts. There was also 1 report of brain bleed/ARIA/stroke without additional information regarding the final diagnosis despite follow up attempts.

Additionally, there were 2 reports of cerebral haemorrhage following a fall which due to the traumatic aetiology of the events are unlikely to represent ICH related to lecanemab. Of these 2 reports, 1 report was an intraventricular haemorrhage and slight brain swelling which was described on MRI as mild brain swelling and possible small bleed and 1 report of a patient who developed mild, asymptomatic ARIA-H (microhaemorrhages) and 1 month later fell, developed confusion and imbalance, and was found to have a left medial temporo-occipital ICH.

The remaining 4 reports include 1 fatal haemorrhagic stroke which is discussed in Section 0. The other 3 cases are described below:

- A spontaneous consumer report which has not been medically confirmed described a patient who was hospitalised in the cardiac intensive care unit 4 days after starting lecanemab and 2 days later, during the hospitalisation, was found to have a brain bleed. The action taken with lecanemab, *APOE4* status, presence of symptoms, and details of the treatment provided in the cardiac intensive care unit (ICU) are not known.

- A spontaneous physician report described [redacted]a *APOE4* noncarrier who had a headache on the day of each of the first 2 lecanemab infusions which resolved the following day. The patient had a CT scan on both occasions, which revealed no abnormalities. 4 days after the second infusion, the patient had a severe headache and fell, striking their head, and was noted to have altered mental status and right sided neglect. CT revealed an ICH in the parietal lobe and the patient was hospitalised. Lecanemab was discontinued. The patient subsequently had a series of "mini strokes" and was transitioned to hospice. The reporter considered the ICH to be possibly related to lecanemab. Past medical history included a "couple" of microhaemorrhages, stroke 20 years earlier, a ministroke 9 months earlier, and a head injury due to a motor vehicle accident. Concomitant medications included aspirin.

- A solicited physician report described [redacted], *APOE4* status unknown, who developed balance difficulties approximately 2 months after starting lecanemab. An MRI showed a small haemorrhagic stroke in the left parietal lobe, multiple small ischemic strokes, and multiple microhaemorrhages,

all of which were considered medically important by the reporter. Lecanemab was interrupted. The outcome of the events was not recovered. The reporter considered the events to be probably related to lecanemab. Past medical history and concomitant medications were not known.

While the number of patients treated commercially with lecanemab is not known and a reporting rate based on patient-years of exposure is likely to overstate the incidence based on actual patients treated, considering the known background rate of ICH in patients with AD, the rate of reports that are likely to represent nontraumatic ICH>1 cm (based on an estimated reporting rate of 0.001 per patient-year of exposure) appears consistent with that observed clinical development programme and the population being treated.

There have been 3 reports of ICH in the Japanese postmarketing setting. One report had limited information but noted that the patient had "a strange sensation in the left head" and was found to have an ICH, size not specified. The other two reports were confirmed ICH and are detailed below:

- One report described a [redacted] *APOE4* heterozygous carrier who was found to have an ICH and concurrent ARIA-E on an MRI performed 27 days after initiating therapy with lecanemab. The ICH was classified as medically important by the treating physician. The patient was asymptomatic and did not require hospitalisation or other treatment. Lecanemab was interrupted. ~3 months later, the patient was recovering from the ICH and lecanemab was resumed. The patient was not taking any concomitant antithrombotic medications.

- A second report described a [redacted] *APOE4* noncarrier with MCI due to AD who had a headache and decreased appetite over the course of the 1st month after starting treatment with lecanemab. An MRI was performed due to the presenting symptoms and the patient was diagnosed with a cerebral haemorrhage of 2 cm and the patient was hospitalised. The patient did not have concurrent ARIA-E. Lecanemab was discontinued, and the event was not recovered. The patient did not receive any treatment for the event and was not taking any concomitant antithrombotics.

(4) Proposed Risk Minimisation Measures and Additional Pharmacovigilance for ICH>1 cm in Diameter

ICH>1 cm events are detectable, and the applicant has proposed a number of activities to support HCPs in the monitoring for these events and to ensure HCPs are aware of appropriate patient management if these events occur. This patient management includes both radiographic and symptomatic events. Further details on the HCP Guide and Checklist, as well as the Patient Alert Card, are provided in the RMP.

A follow up questionnaire to be used by HCPs when reporting postmarketing ARIA-E, -H and ICH>1 cm events is proposed to support the characterisation of these events, with this data to be reported in PSURs.

A PASS to further characterise ARIA-E, -H and ICH>1 cm, effectiveness of RMMs, and drug utilisation is also proposed.

Routine Risk Communication

- SmPC Section 4.2
  - Treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease in centres with timely access to MRI
  - Obtain a recent (within 6 months) baseline brain MRI prior to initiating treatment with lecanemab to evaluate for pre-existing ARIA.

- Obtain an MRI prior to the 5th, 7th, and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed including an MRI
- Requires dose suspension until MRI demonstrates radiographic stabilisation and symptoms, if present, resolve.
- Lecanemab should be permanently discontinued if intracerebral haemorrhage greater than 1 cm in diameter occurs.

- SmPC Section 4.3
  - Contraindication for patients with MRI findings suggestive of severe CAA, defined as >4 microhaemorrhages or an area of superficial siderosis on pre-treatment MRI.

- SmPC Section 4.4
  - Administration of a thrombolytic agent (e.g., tissue plasminogen activator) during lecanemab use should be carefully monitored as the use of these agents may increase the risk of bleeding in the brain.
  - The presence of an APOE4 allele is also associated with CAA, which has an increased risk for intracerebral haemorrhage.
  - Additional caution should be exercised when considering the administration of anticoagulants to a patient already being treated with lecanemab.

Healthcare Professional Guide and Checklist

The guide reinforces the need for enhanced clinical vigilance during the first 14 weeks of treatment for ARIA. Where a patient experiences a symptom, HCPs are recommended to undertake clinical evaluation including MRI. Recommendations for dosing interruptions, in line with the SmPC are reiterated. The guide highlights that caution should be exercised when considering LEC10-BW use where there is an increased risk of ICH>1 cm including 1) presence of *APOE4* alleles and, 2) signs suggestive of CAA on pre-treatment MRI. The guide and checklist highlight the risks associated with thrombolytic and anticoagulants (Section 0).

Patient Alert Card

The Patient Alert Card focuses on providing targeted information on the potential clinical symptoms in the setting of ARIA and to reinforce the importance of seeking medical advice in a timely manner, thus promoting patient safety.

Follow-Up Questionnaire

To monitor the nature of reports of suspected ARIA in postmarketing, an ARIA specific questionnaire has been developed to further characterise the risk.

ARIA Education

The Applicant will be working with the European AD specialists and neuroradiologists to increase ARIA awareness and provide educational materials (Section 0).

5.1.1.3.8. Deaths Concurrent With ARIA-E, -H, or Intracerebral Haemorrhage >1 cm in Diameter

IIn the Core, there were no deaths on LEC10-BW and 1 death (0.0008 per PY of exposure) with concurrent ICH>1 cm in PBO: 1 (noncarrier) subject. In the OLE Phase, there were 3 deaths (0.0009 per PY of exposure) with concurrent ARIA-E, -H, or ICH> 1 cm: 1 (homozygous APOE4 carrier) subject

with multiple ICH>1 cm after tissue plasminogen activator (tPA); 1 (noncarrier) subject with subacute ICH>1 cm; and 1 (homozygous APOE4 carrier) subject with severe ARIA-E and concurrent ARIA-H microhaemorrhage. Overall, deaths, and deaths with concurrent ARIA, when adjusted to patient-years of exposure, are similar for LEC10-BW and PBO. The summary of deaths that follows contains previously submitted analyses.

(1) ARIA-E or ARIA-H

There were 3 subjects treated with LEC10-BW who had death concurrent with ARIA-E or -H:

- Subject [redacted] was a noncarrier [redacted] who received PBO in the Core and LEC10-BW in the OLE Phase. The subject was taking acetylsalicylic acid 81 mg during the events described herein. On Extension Day 116, the subject reported trauma to both arms and increased confusion. An adverse event of ARIA-H was reported based on the symptoms and the MRI finding. An associated event of ARIA-E was reported on the same day. Day 118, MRI showed the presence of a left occipital ICH. On Day 124, the subject experienced chest pain and shooting pain in the left arm. The subject was submitted to the ER and diagnosed with a non-ST elevated myocardial infarction. The subject was treated with heparin, which was discontinued due to occipital ICH. The subject then received aspirin and nitroglycerin and when condition improved, was discharged from hospital. On Day 128, the subject experienced transient ischemic attacks. During attacks the subject's speech was affected, and experienced right-side weakness. The subject was enrolled in hospice and was prescribed lorazepam. On Day 143 the subject died. The cause of death was reported as symptomatic left occipital intracerebral haemorrhage by the investigator.

- Subject [redacted] was a homozygous *APOE4* [redacted] who received PBO in the Core and LEC10-BW in the OLE Phase. The subject was taking acetylsalicylic acid 325 mg during the events described herein. The subject reported symptoms of severe seizure, moderate hemiplegia, and moderate dysarthria on Extension Day 38. On Day 38, the subject experienced a sudden onset of slurred speech, started to gaze left and had left side weakness. The subject was evaluated as a potential acute stroke and was determined not to be a candidate for tPA. The subject was hospitalised for a possible seizure and possible cerebrovascular accident (CVA). The subject was noted to be in paroxysmal atrial fibrillation on telemetry. The subject was started on aspirin, Keppra (levetiracetam), and empirical antibiotics. AEs of radiographically moderate ARIA-E was reported on Day 40. The ARIA-E was reported as severe, serious (hospitalisation), symptomatic, and related to study drug. An associated adverse event of ARIA-H was also reported on Extension Day 40, which was reported as severe, serious (hospitalisation), symptomatic, and related to study drug. CT brain perfusion scan/CTA was performed which showed extensive atherosclerotic calcification of the carotid arteries, no evidence of large vessel occlusion and symmetric perfusion without evidence of cerebral ischemia. An EEG was performed, which showed frontal dominant rhythmic delta activity, possibly due to structural abnormalities, diffuse background slowing consistent with metabolic encephalopathy and no epileptiform activity or evidence of focal cerebral dysfunction. Subject was started on IV heparin for atrial fibrillation. On Day 43, the subject developed respiratory distress and was transitioned to comfort measures including discontinuation of BiPAP and died due to possible CVA, possible seizure, and possible cerebral oedema. This case was published (Solopova, et al., 2023).

- Subject [redacted], homozygous *APOE4* carrier who received PBO in Study 301 Core and LEC10-BW in the OLE Phase. Screening MRI on 08 Oct 2020 revealed no ARIA-E, no microhaemorrhages, no microhaemorrhages, and no superficial siderosis. The subject received the 3rd dose (last dose) of LEC10-BW and, few days later, during dinner, the subject had a blank stare and was talking incoherently. Soon thereafter, speech became garbled, and partner suspected that the subject was

having a stroke. The subject was transported to an ER. A CT scan confirmed an occlusive left sided cerebrovascular accident (no MRI was performed at initial presentation). The stroke code was activated, and the subject was tPA 8 mg IV therapy in the ER. 8 minutes after administration of tPA, the subject started to experience headaches. The subject became acutely agitated after another 40 minutes of tPA therapy. The CT scan revealed possible bilateral ICH with subarachnoid haemorrhage. The neurology team stopped tPA treatment and administered cryoprecipitate and tranexamic acid to reverse tPA therapy. Haldol 1 mg was given for agitation. EEG revealed seizure activity; Ativan (lorazepam) 2 mg and Keppra (levetiracetam) 2 mg was given to control the seizure. The systolic blood pressure was greater than 200 mmHg and was treated with nicardipine infusion. The subject was transferred to neurology ICU where the subject remained agitated. Subsequently, the subject had a worsening in encephalopathy and respiratory deterioration, requiring intubation. The ICU and stroke team confirmed with the subject's family that the subject did not wish to remain on life support indefinitely. The subject was to be weaned off the ventilator with eventual extubation. An MRI revealed extensive multicompartmental intracerebral haemorrhage, subarachnoid haemorrhage, and a right intraventricular haemorrhage, with 5 mm leftward midline shift and bilateral uncal herniation. The subject died shortly after extubation. The acute multifocal ICH post tPA resulted in the outcome of death. An autopsy was performed, and the cause of death was attributed to non-traumatic ICH. The autopsy showed extensive multifocal intraparenchymal haemorrhage, CAA, "high" AD neuropathologic changes, and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within (but not outside) the blood-vessel walls. There was no vascular territory infarct apart from an agonal lesion in the right posterior limb of the internal capsule. The patient otherwise had non-significant cerebrovascular or cardiovascular disease apart from a patent foramen ovale. The investigator classified the event of cerebrovascular accident to be not related to study drug. The investigator classified the event of cerebral haemorrhage to be related to study drug. The autopsy report notes necrotizing histiocytic vasculitis and parenchymal microglial reaction with plaque phagocytosis in the brain, which predisposed to the ICH following tPA administration. Additionally, the autopsy report noted a lack of vascular territory ischemic infarct apart from an agonal lesion in the right posterior limb of the internal capsule, raising the possibility that the necrotizing vasculitis was the cause of symptoms, which mimicked an ischemic stroke. Given that there have been reports of fatal large catastrophic ICH after tPA administration in patients with CAA in the absence of anti-amyloid therapy, and considering that there have been reports in the literature of vasculitis associated with cerebral amyloid angiopathy in the absence of anti-amyloid therapy, the event of acute multifocal ICH post tPA was classified by the applicant as "Not related" to the study medication. This case was published in New England Journal of Medicine and the Journal of Alzheimer's Disease (Castellani, et al., 2023; Reish, et al., 2023).

Postmarketing Experience (Up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

There have been 3 reports of deaths in patients who experienced ARIA-E, including 2 reports of concurrent ARIA-E and ARIA-H, all from spontaneous sources in the US. The reports of deaths in patients with ARIA-E occurred early in treatment with 2 reports in *APOE4* carriers (1 homozygous *APOE4* carrier and 1 heterozygous *APOE4* carrier) and 1 where *APOE4* status was not known. The timing for these events was consistent with the timing observed for ARIA-E in general and there was no pattern, such as *APOE4* genotype or stage of disease at lecanemab initiation, to suggest a particular subgroup at increased risk.

A summary of these reports is provided below:

- This spontaneous healthcare professional report [redacted] describes an heterozygous *APOE4* carrier who experienced symptomatic severe ARIA-E, severe ARIA-H (microhaemorrhage), and moderate superficial siderosis (reported symptoms included weakness, disorientation, unable to tell right from left, loss of appetite, problem with depth perception, unable to perform basic tasks, rash, and confusion) ~ 1 month after starting lecanemab. One week later, the patient was hospitalised with status epilepticus. Lecanemab was permanently discontinued, and the patient was treated with prednisone and levetiracetam with improvement in the seizures and the symptoms of ARIA. One month later, the patient was hospitalised for a second episode of status epilepticus, showed no improvement and was transitioned to hospice and passed away. The treating physician reported that the cause of death was not known but considered the death to be possibly related to lecanemab. It was unknown if an autopsy was performed. Past medical history was significant for hyperlipidaemia, hypertension, and past alcohol use. There was no history of seizures. Concomitant medications included simvastatin, fenofibrate, and fish oil.

- This spontaneous physician report[redacted] describes *APOE4* status unknown, who experienced aphasia and left sided weakness after the 3rd dose of lecanemab. The patient was taken to the ER and confirmed to have experienced ARIA-E and was hospitalised. The action taken with lecanemab was not known. Nine days later, the patient died. The cause of death was not known. The outcome of ARIA-E at the time of death was ongoing. It was unknown if an autopsy was performed. Past medical history and concomitant medications were not provided.

- This spontaneous healthcare professional report [redacted] describes a homozygous *APOE4* carrier who had confusion, memory loss, and word finding difficulty following the 3rd dose of lecanemab. An MRI was performed, and the patient was diagnosed with ARIA-E and ARIA-H and lecanemab was discontinued. Two days later, the patient was hospitalised following a seizure and died 5 days later. An autopsy was not performed. Past medical history and concomitant medications were not provided.

- While the number of patients treated commercially with lecanemab is not known and a reporting rate based on PYs of exposure is likely to overstate the incidence based on actual patients treated, considering the estimated exposure of more than 3125 patient-years (estimated exposure based on over 180,000 vials distributed), the rate of fatal ARIA-E and -H (based on an estimated reporting rate of 0.001 per PY of exposure) is consistent with that observed in the clinical development programme.

(2) Intracerebral Haemorrhage >1 cm in Diameter

There was 1 subject receiving PBO who had a death concurrent with ICH>1 cm:

- Subject [redacted] was a noncarrier [redacted] who received PBO in the Core. The subject was taking acetylsalicylic acid 81 mg during the events described herein. Screening MRI showed 1 left frontal lobe microhaemorrhage and focal white matter disease with no changes noted on subsequent MRIs. No ICH>1 cm were reported. The subject was admitted for confusional state on Day 361. The subject was discharged the following day (Day 362). Confusional state was ongoing at the time of death. On Day 366, the subject's caregiver reported that the subject has not seen a primary care physician or been taking any medication for 8 months. The subject and family would have visited their primary care physician in the following week and would have taken a decision if the subject had to continue in the study. After this, on an unknown date while hospitalised, brain MRI showed a lesion on the temporal lobe that led to haemorrhage. Since this event of ICH was reported with an unknown onset date; the onset date was imputed as Day 1 per the Clinical Data Interchange Standards Consortium. Further details were not available. On Day 402, the subject died due to ICH. It was unknown if an autopsy was performed.

Postmarketing Experience (Up to 18 Months Experience)

The PV summary contained in this section is new for the re-examination procedure.

There has been 1 fatal spontaneous post-marketing report of ICH> 1 cm from the US:

- A spontaneous physician [redacted]report described a noncarrier who received lecanemab for nearly a year. During that period, the patient had multiple MRIs without ARIA-E or ARIA-H. The patient was hospitalised for a large left parietal and occipital haemorrhagic stroke with 3 mm midline shift. Lecanemab and co-suspect medications donepezil, memantine, and buspirone were discontinued. The patient died due to the haemorrhagic stroke. An autopsy was not performed. The reporter considered the event to be possibly related to lecanemab. Past medical history was significant for cerebrovascular brain disease, chronic kidney disease stage 3, depression, anxiety, former smoker and transient ischemic attack. Concomitant medications included modafinil, aspirin, and tolterodine.
- While the number of patients treated commercially with lecanemab is not known and a reporting rate based on PYs of exposure is likely to overstate the incidence based on actual patients treated, considering the considering the known background rate of ICH in patients with AD and an estimated exposure of more than 3125 patient-years (estimated exposure based on over 180,000 vials distributed), the rate of fatal ICH >1 cm (based on an estimated reporting rate of 0.0003 per patient-year of exposure) is consistent with that observed in the clinical development programme.

5.1.1.3.9. Assessment of the Long-Term Consequences of ARIA

Data from both Study 301 and the gantenerumab arm in the DIAN-TU-001 study (both up to 36 months of treatment) show that ARIA-E and -H do not adversely impact efficacy and are not associated with accelerated long-term progression, irrespective of *APOE4* genotype. The Applicant acknowledges that the CHMP seeks further long-term data on patients who have experienced ARIA-E and -H, and therefore agreed to include "acceleration of disease progression due to ARIA induced brain atrophy" as an "important potential risk" in the RMP, with data to evaluate this risk being generated from the Study 301 OLE Phase (early AD population) and Study 303 (preclinical AD population).

The analytic approaches described in this section are supported by the fact that ARIA-E with LEC10-BW occurs early in treatment (~90% of all ARIA occurs within first 6 months of treatment), which allowed subjects to be followed for 12 months or longer after the initial ARIA-E event within Study 301 Core. For example, in LEC10-BW, 193 patients had an ARIA-E event, and 161 patients had follow-up with a mean exposure of 12.2 months after the onset of the 1st ARIA-E event.

The long-term consequences summary that follows contains both previously submitted and new analyses.

(1) Potential for Accelerated Long-Term Progression

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Study 301 Core (18 Months Placebo-Controlled Treatment)

The Applicant evaluated the proportion of LEC10-BW subjects that progressed beyond different thresholds of CDR-SB, based on whether or not they experienced ARIA over 18 months (PBO is included for reference). CDR-SB thresholds ranging from 0.5 to 6.0 were evaluated, with these thresholds also evaluated by genotype.

Figure 32 provides the proportion of LEC10-BW subjects that progressed beyond 3 or more points on CDR-SB for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population; a threshold of 3.0 on the CDR-SB represents twice the PBO decline (1.66) reported in Study 301 Core.

Irrespective of threshold used, or whether the events evaluated are ARIA-E, -H or concurrent ARIA-E, -H, there is no evidence that subjects with these events have accelerated cognitive and functional decline compared to those without these events.

Individual genotypes are presented in the additional appendices provided by the applicant.

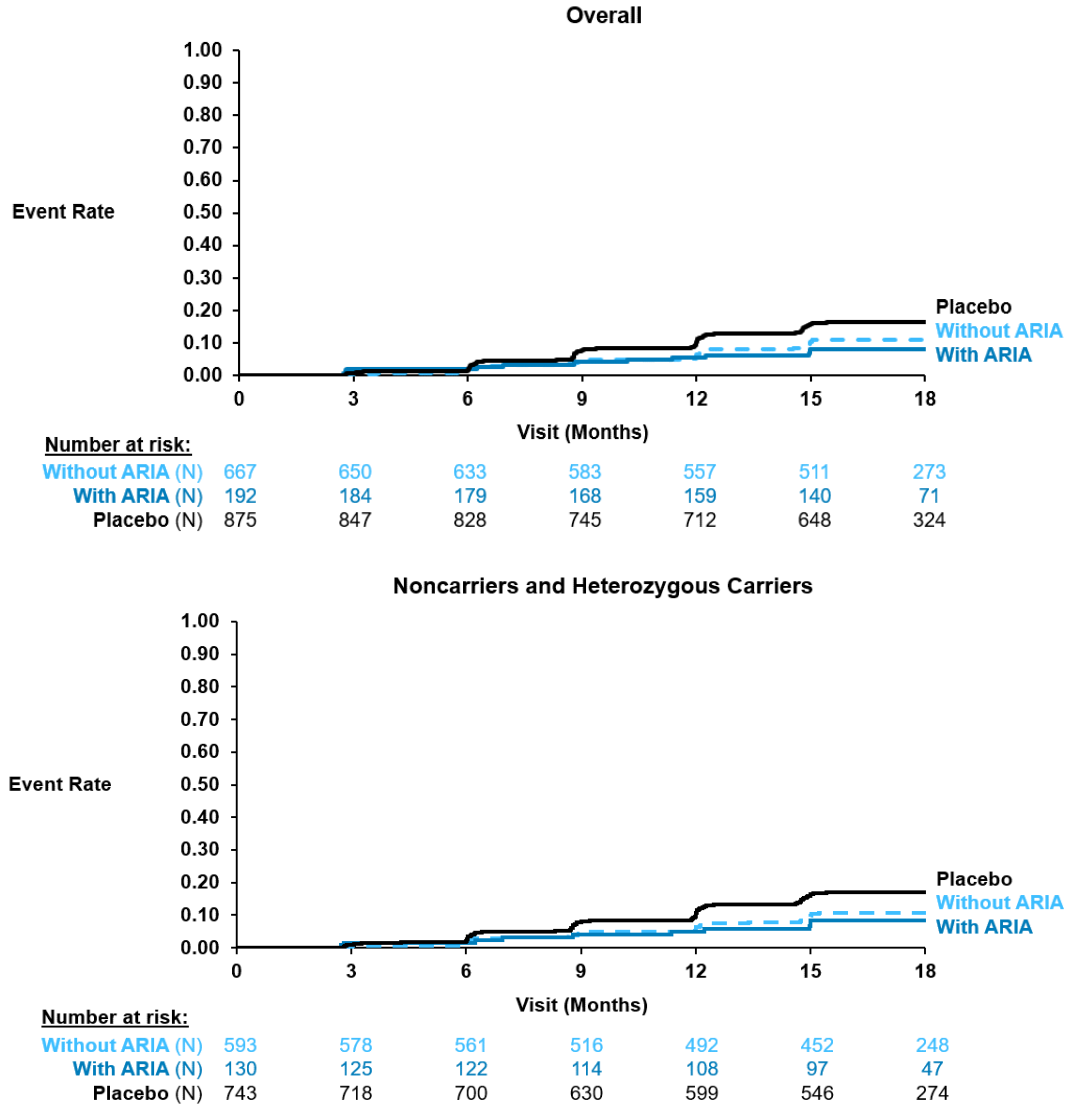


Figure 32. Time to worsening of CDR-SB by 3.0 points for subjects with and without ARIA in LEC10-BW and PBO – study 301 core (mITT)

Time to worsening of CDR-SB scores is defined as time in days from randomisation to a confirmed worsening of the CDR-SB scores (i.e., the 1st worsening where there is an increase from baseline by at least 3.0 points on the CDR-SB score, in 2 consecutive visits). Time to worsening of CDR-SB scores will be censored at the date of last CDR assessment if no event. Time in months is calculated by time in days divided by 30.417.
APOE4 = apolipoprotein E4 variant, ARIA = amyloid-related imaging abnormalities, CDR-SB = Clinical Dementia Rating – Sum of Boxes, mITT = modified intent to treat, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.
Source: Appendix 1 Figure 14.3.2.6.5.1nh.

Study 301 Open Label Extension (36 Months Total Treatment)

The same analyses were performed with data through 36 months for the LEC10-BW Treated Period. Figure 33 provides the proportion of LEC10-BW subjects that progressed beyond 3.0 or more points on CDR-SB, based on whether or not they experienced ARIA over 36 months. CDR-SB cutoffs ranging from 0.5 to 6.0 were explored with all showing similar results are seen for the 3-point cut off.

Again, irrespective of threshold used, or whether the events evaluated are ARIA-E, -H, or concurrent ARIA-E, -H, there is no evidence that subjects with these events have accelerated cognitive and functional decline compared to those without these events.

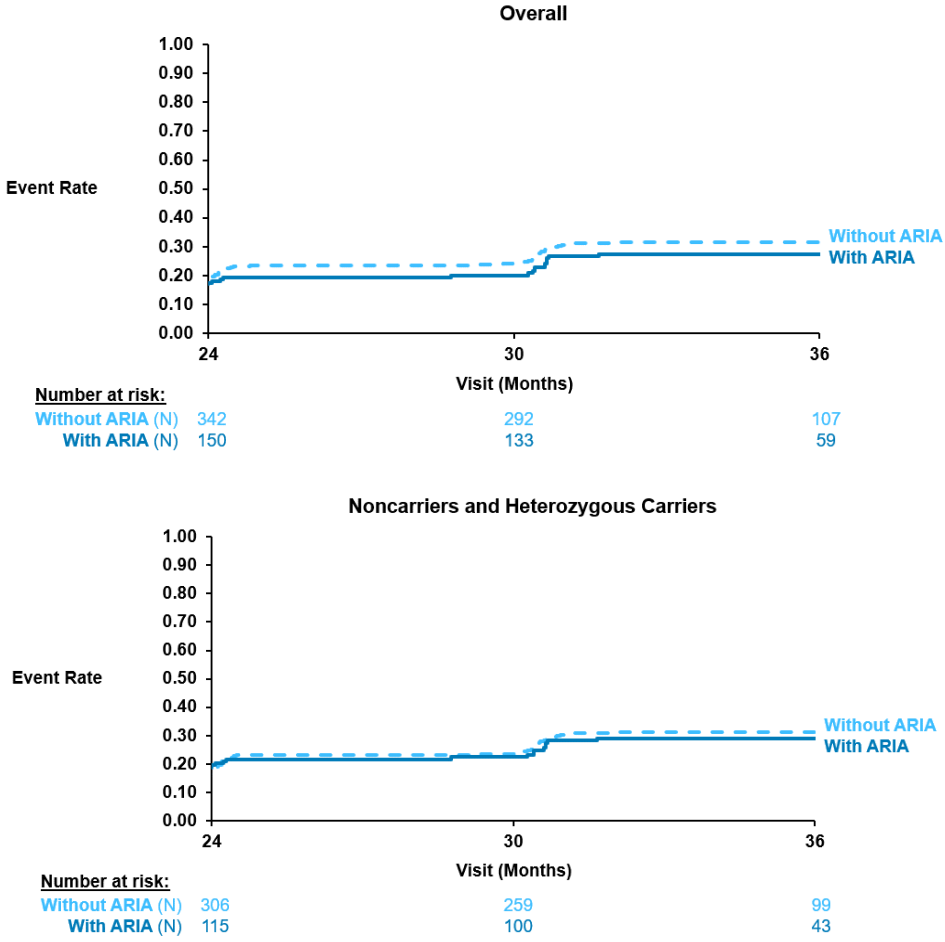


Figure 33. Time to worsening of CDR-SB by 3.0 points through 36 months for subjects with and without ARIA in LEC10-BW – study 301 core and OLE pPhase (mITT)

Time to worsening of CDR-SB scores is defined as time in days from randomisation to a confirmed worsening of the CDR-SB scores (i.e., the 1st worsening where there is an increase from baseline by at least 3.0 points on the CDR-SB score, in 2 consecutive visits). Time to worsening of CDR-SB scores will be censored at the date of last CDR assessment if no event. Time in months is calculated by time in days divided by 30.417.
APOE4 = apolipoprotein E4 variant, ARIA = amyloid-related imaging abnormalities, CDR-SB = Clinical Dementia Rating – Sum of Boxes, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, OLE = open-label extension.
Source: Appendix 1 Figure 14.3.2.6.5.1nh.

Gantenerumab Data From the DIAN-TU-001 Open Label Extension (Up to 36 Months Treatment)

The information contained herein was presented at AAIC 2024 (Bateman, 2024).

DIAN-TU-001 is a PBO-controlled, double-blind platform trial with a 36-month OLE Phase in subjects with a known mutation or 'at risk' for dominantly inherited AD treated with either gantenerumab, solanezumab, or PBO. Gantenerumab data from the 36-month OLE Phase is consistent with what was seen in Study 301; the presence of ARIA-E or ARIA-H does not lead to a greater decline in cognitive or functional abilities (Figure 34).

[figure omitted]

Figure 34. Mean change from baseline for CDR-SB between those with and without ARIA-E (left) or ARIA-H (right) treated with gantenerumab – DIAN-TU-001

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality- haemorrhage , CDR-SB = Clinical Dementia Rating-Sum of Boxes, OLE = open-label extension.
Source: AAIC (Bateman, 2024).

(2) Accelerated Brain Volume Loss

Accelerated brain volume loss following anti-amyloid therapies for AD has been extensively discussed in the peer-reviewed Lancet Neurology publication by Belder, et al., 2024. The applicant provided data for the Study 301 Core in Response to 2nd D180 Question 28 and Response to 1st D180 Question 24 Section 1.5.3.

The relevant extracts (verbatim) from the publication are:

"…trials of anti-amyloid monoclonal anti-bodies with successful amyloid removal have consistently shown excess brain volume changes of a magnitude less than 1% of brain volume. A reasonably consistent pattern of volume change has emerged, with proportionally greater excess volume change in the ventricular system than whole brain volume, and in the cortex compared with the brain as a whole. Importantly, there is no consistent evidence for excess hippocampal volume loss. Indeed, in trials showing slowing of cognitive decline, there was slight attenuation of hippocampal volume loss."

"Given that therapies that induce the most amyloid clearance are associated with the greatest change in cerebral and ventricular volume, could the excess volume loss be explained by removal of amyloid β pathology? Although the total mass of amyloid β peptide in the brain of people with Alzheimer's disease has been estimated to be far less than is necessary to account for these volume changes, it is important to note that amyloid plaques occupy a volume much greater than that due to the amyloid β protein itself. Each plaque also contains a host of other proteins and dystrophic neurites, and is associated with reactive glia and fluid, all of which occupy volume."

[figure omitted]

Figure 35. Whole brain volume and ventricular volume outcomes in key trials, shown as treatment group minus placebo group

Source: Belder, et. al., 2024 Figure 1.

Study 301 Open Label Extension (36 Months Total Treatment)

The analyses and content contained in this section are new for the re-examination procedure.

Figure 36 shows the relationship between changes in amyloid PET with whole brain volume loss for early start versus late start LEC10-BW treatment at 30 months (note: amyloid PET assessment in the OLE Phase is every 12 months; therefore, 36-month data are not available) in Study 301.

Consistent with the 18-month data, greater brain volume loss is seen with more amyloid removal.

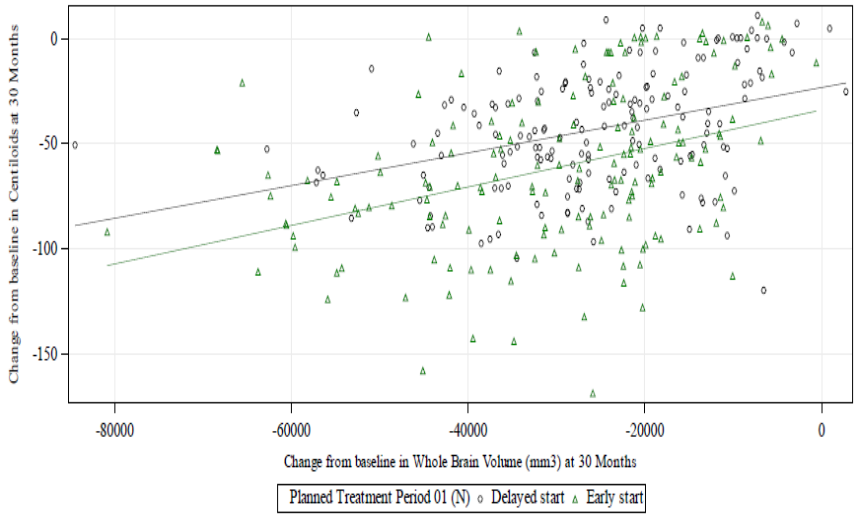


Figure 36. Scatter plot of change from baseline at 30 months between vMRI and amyloid PET using Centiloids - study 301 core and OLE phase - PD analysis set (amyloid PET) and PD analysis set (vMRI)

PET = positron emission tomography, OLE = Open-label Extension, PD = pharmacodynamic, vMRI = volumetric magnetic resonance imaging.
Early start group subjects are those assigned to lecanemab (10 mg/kg biweekly) in Core Study, and delayed start group subjects are those assigned to placebo in Core Study.
Source: Appendix 1 Figure 14.3.2.6.6.1nh.

Similarly for clinical outcome correlations (Figure 37), the early start LEC10-BW correlation lines are shifted toward improvement relative to delayed start LEC10-BW across the range of observed changes in brain volume. For any level of volume loss on lecanemab, there is less decline than the corresponding level of volume loss in delayed start LEC10-BW at 36 months.

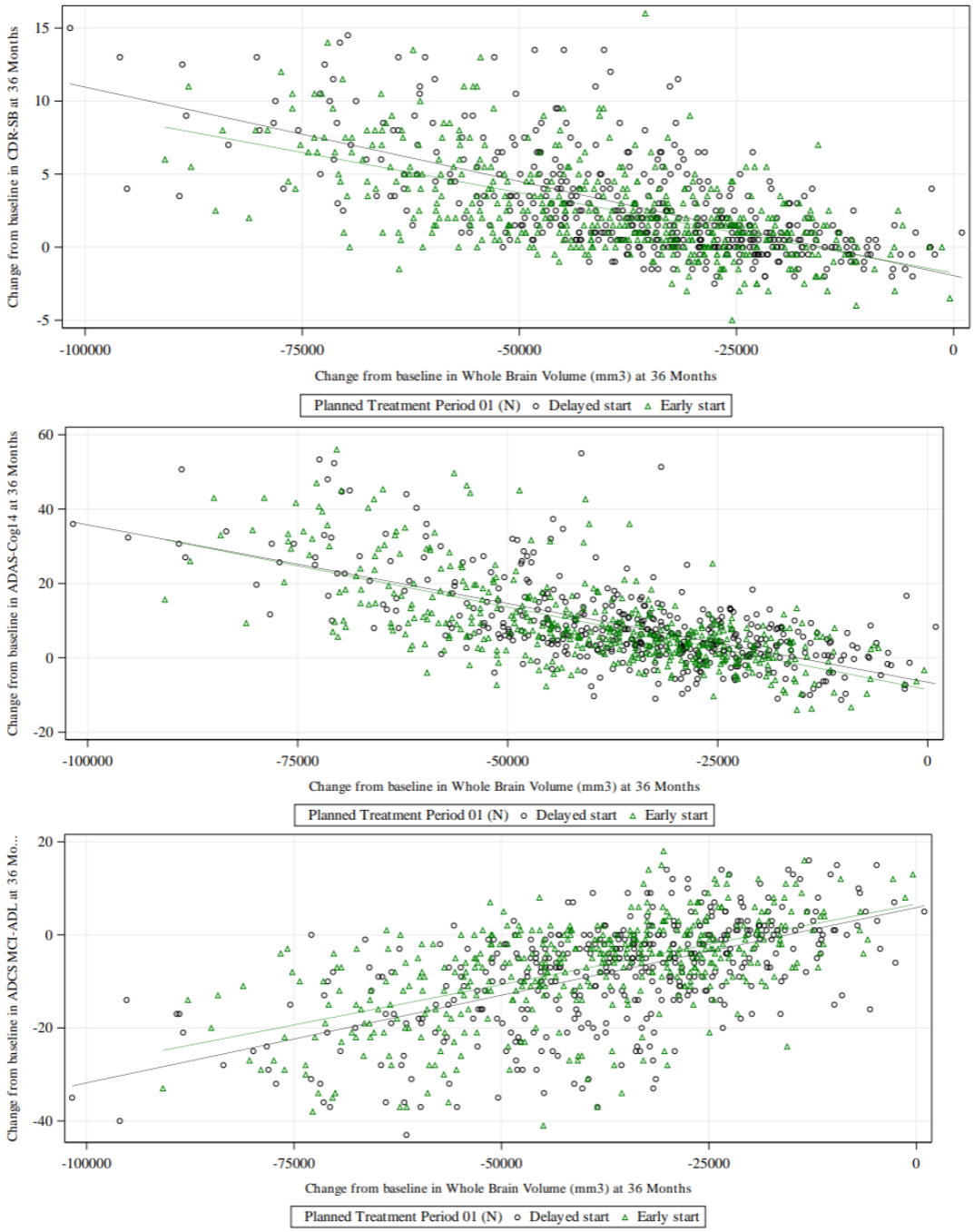


Figure 37. Scatter plot of change from baseline at 36 months between vMRI and clinical endpoints (CDR-SB [top], ADAS-Cog14 [middle], ADCS-MCI-ADL [bottom]) study 301 core and OLE phase - (mITT) and PD analysis set (vMRI)

PET = positron emission tomography, OLE = Open-label Extension, PD = pharmacodynamic, vMRI = volumetric magnetic resonance imaging.
Early start group subjects are those assigned to lecanemab (10 mg/kg biweekly) in Core Study, and delayed start group subjects are those assigned to placebo in Core Study.
Source: Appendix 1 Figure 14.3.2.6.6.2nh, Figure 14.3.2.6.6.3nh, and Figure 14.3.2.6.6.4nh.

Brain Volume Differences Relative to PBO are Associated With Better Clinical Outcomes

Analysis across all clinical studies of AD therapeutics (ten Kate, et al., 2024) demonstrate that the class of amyloid removing therapies show discordance between brain volume loss and clinical outcomes, with

an overall pattern of a treatment-related slowing of clinical decline relative to PBO being accompanied by accelerated brain volume loss relative to PBO (Figure 38) for treatments that clear amyloid from the brain.

[figure omitted]

Figure 38. Scatter plot showing the relationship between published treatment effects on clinical and imaging outcomes

Source: Adapted from ten Kate, et al., 2024.

Across anti-amyloid therapies, brain volume loss appears to be related to the extent of amyloid removal, spares the hippocampus, and is not associated with worse clinical outcomes (at a group-level) (Belder, et al., 2024). This is consistent with the results from the lecanemab clinical programme.

(3) Proposed Risk Minimisation Measures and Additional Pharmacovigilance for Long Term Consequences of ARIA

Routine Risk Communication

- SmPC Section 5.1
  - An increase in brain volume loss relative to placebo was observed with anti-β amyloid antibodies, including lecanemab. The clinical relevance of this observation is currently unclear, given the results on clinical and other biomarker endpoints in Study 301.

Additional Pharmacovigilance

To further characterise the important potential risk "acceleration of disease progression due to ARIA induced brain atrophy," the applicant has proposed to provided data from ongoing studies Study 301 OLE Phase and Study 303.

- Study 301 OLE Phase is an open-label study in individuals with early AD, as 31 Mar 2024, 464 subjects have been treated for ≥36 months.
- Study 303 is a 4-year study in individuals with preclinical AD and given the long duration of a PBO control (4 years) the applicant proposes to use this study characterise this important potential risk as described in the current RMP. As of 30 Apr 2024, 1168 subjects have been randomised.

5.1.1.3.10. Assessment of the Impact of Dose Pauses on ARIA

The analyses and content contained in this section are new for the re-examination procedure.

In Study 201 Core, all ARIA E cases resulted in discontinuation per protocol, regardless of clinical (i.e., asymptomatic or symptomatic) or radiographic severity. However, these subjects were permitted to enrol into the OLE Phase. Notwithstanding when subjects discontinued due to an ARIA-E event in the Core, there was a Gap Period between the end of Study 201 Core and the OLE Phase (24-month average, range: 9 to 59 months). Therefore, for these subjects that experienced an ARIA-E event during the Core and entered the OLE Phase, there was a prolonged treatment pause.

A comparison between Study 201 and Study 301 (where there was no Gap Period between the Core and OLE Phase), provides an opportunity to examine the impact of prolonged treatment pauses on ARIA.

(1) Study 201

ARIA-E

In Study 201 Core, 46 subjects had ARIA-E in lecanemab-treated groups (regardless of dose). Of these, 4 subjects subsequently entered the OLE Phase. The mean treatment gap for these subjects was 40.0 months. Of these subjects:

- 3/4 (75%) subjects experienced recurrent ARIA-E (1 subject treated with LEC10-BW and 2 subjects treated with LEC10-M during the Core).
- 1/4 (25%) subjects did not experience recurrent ARIA-E.

The change in severity of the ARIA for these subjects who experienced a recurrent event following a dosing pause is described in Table 86.

To provide a comparison, in Study 301 Core, there were 113 cases of treatment-emergent ARIA-E. Amongst these subjects, 96/113 continued treatment. Of these subjects, 28/96 (29%) experienced a recurrence of ARIA-E.

Table 86. Subjects experiencing a recurrent ARIA-E event following a prolonged treatment pause – study 201

Subject ID/ Core group/ genotype	Event	Start Date	End Date	Radiographic severity	Symptom status
[redacted] LEC10-M/ Heterozygous *APOE4* carrier	ARIA-E	23May2016	01Nov2016	Mild	Asymptomatic
	Last infusion date in Core	**17Jun2016**	-	-	-
	OLE start date (Gap=1037 days)	**19Apr2019**	-	-	-
	ARIA-E	14Jun2019	22Jan2020	Moderate	Asymptomatic
	ARIA-H MH	04Oct2019	Ongoing	Moderate	Asymptomatic
[redacted] LEC10-M/ Homozygous *APOE4* carrier	ARIA-E	11Oct2016	05Jan2017	Mild	Asymptomatic
	Last infusion date in Core	**11Oct2016**	-	-	-
	OLE start date (Gap=1114 days)	**29Oct2019**	-	-	-
	ARIA-H MH	13Apr2022	Ongoing	Mild	Asymptomatic
	ARIA-E	11Oct2023	17Nov2023	Mild	Asymptomatic
	ARIA-E	17Nov2023	27Mar2024	Moderate	Asymptomatic
[redacted] LEC10-BW/ Heterozygous *APOE4* carrier	**Last infusion date in Core**	**08Sep2014**	-	-	-
	ARIA-E	17Sep2014	08Dec2014	Mild	Asymptomatic
	OLE start date (Gap=1817 days)	**29Aug2019**	-	-	-
	ARIA-E	10Oct2019	08Nov2019	Moderate	Asymptomatic
	ARIA-E	08Nov2019	06Dec2019	Severe	Asymptomatic
	ARIA-E	06Dec2019	03Jan2020	Moderate	Asymptomatic
	ARIA-H SS	06Dec2019	Ongoing	Mild	Asymptomatic
	ARIA-E	14Feb2020	28May2020	Mild	Asymptomatic

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality- hemorrhage , LEC10-BW = lecanemab 10 mg/kg biweekly, LEC10-M = lecanemab 10 mg/kg monthly, MH = microhaemorrhage, OLE = open-label extension, SS = superficial siderosis.
Treatment-emergent adverse events are presented. For 201OLE, radiographic severity of microhemorrhage is based on the number of new microhemorrhage from OLE baseline.

ARIA-H

In Study 201 Core, 57 subjects had ARIA-H with lecanemab (all dose groups). Of these, 7 subjects subsequently entered the OLE Phase. The mean treatment gap for these subjects was 19.4 months. Of these subjects:

- 2/7 (28.6%) subjects experienced recurrent ARIA-H (1 subject treated with lecanemab 5 mg/kg biweekly [LEC5-BW] and 1 subject treated with lecanemab 5 mg/kg monthly [LEC5-M] during the Core).
- 5/7 (71.4%) subjects did not experience recurrent ARIA-H.

To provide a comparison, in Study 301, there were 152 cases of treatment-emergent ARIA-H. Amongst these subjects, 125/152 continued treatment. Of these subjects 57/125 (46%) experienced a recurrence of ARIA-H.

The change in severity of the ARIA for subjects who experienced a recurrent event after a dosing pause of at least 6 months is described in Table 87.

Table 87. Subjects experiencing a recurrent ARIA-H event after a prolonged treatment pause – study 201

Subject ID/ Core group/ genotype	Event	Start Date	End Date	Radiographic severity	Symptom status
[redacted] LEC5-M/ Heterozygous *APOE4* carrier	**Last infusion date in Core**	**06Dec2017**	-	-	-
	ARIA-H MH	07Dec2017	Ongoing	Mild	Asymptomatic
	OLE start date (Gap=413 days)	**22Jan2019**	-	-	-
	ARIA-E	06Mar2019	28Mar2019	Moderate	Asymptomatic
	ARIA-H MH	06Mar2019	Ongoing	Mild	Asymptomatic
	ARIA-E	28Mar2019	02May2019	Moderate	Symptomatic
	ARIA-H SS	03Apr2019	Ongoing	Severe	Asymptomatic
	ARIA-H MH	03Apr2019	Ongoing	Severe	Asymptomatic
	ARIA-H MH	02May2019	Ongoing	Severe	Asymptomatic
	ARIA-H MH	08Feb2020	Ongoing	Severe	Asymptomatic
	ARIA-H MH	04Jan2022	Ongoing	Severe	Asymptomatic
[redacted] LEC5-BW/ Homozygous *APOE4* carrier	ARIA-H MH	18Jul2017	Ongoing	Mild	Asymptomatic
	Last infusion date in Core	**18Oct2017**	-	-	-
	OLE start date (Gap=491 days)	**20Feb2019**	-	-	-
	ARIA-H MH	03Feb2021	Ongoing	Mild	Asymptomatic

ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality- hemorrhage , LEC5-BW = lecanemab 5 mg/kg biweekly, LEC5-M = lecanemab 5 mg/kg monthly, MH = microhaemorrhage, OLE = open-label extension, SS = superficial siderosis.
Treatment-emergent adverse events are presented. For 201OLE, radiographic severity of microhemorrhage is based on the number of new microhemorrhage from OLE baseline.

(2) Study 301

In Study 301 Core, 113 subjects had ARIA. Of these, 4 subjects had a dose pause of at least 6 months (to allow for re-accumulation of amyloid and biomarkers) after the ARIA-E:

- 2/4 (50%) subjects experienced recurrent ARIA (-E or -H).
- 2/4 (50%) subjects did not experience recurrent ARIA.

ARIA-E

Of the 672 subjects that entered OLE Phase after receiving LEC10-BW treatment for 18 months in Study 301 Core, 12 subjects had ARIA-E for the first time in the OLE Phase.

ARIA-H

In Study 301 Core, 152 subjects had ARIA-H. Of these, 4 subjects had a dose pause of at least 6 months after the ARIA-H or ARIA-E concurrent with ARIA-H. These 4 subjects are the same subjects as described above for ARIA-E. Of these, 2 experienced recurrent ARIA (-E or -H) and 2 subjects did not have a recurrent ARIA.

Of the 672 subjects that entered the OLE Phase after receiving LEC10-BW treatment for 18 months in Study 301 Core, 70 subjects had ARIA-H for the first time in the OLE Phase.

ICH>1 cm

Of the 672 subjects that entered the OLE Phase after receiving LEC10-BW treatment for 18 months in Study 301Core, none had ICH>1 cm in the OLE Phase.

5.1.1.3.11. Overview of Non-ARIA Post-marketing Events

The PV summary contained in this section is new for the re-examination procedure.

While the number of patients treated commercially with lecanemab is not known, it is estimated that the cumulative worldwide exposure of lecanemab is more than 3,700 patient-years distributed (estimated exposure based on over 215,000 vials distributed).

A cumulative summary tabulation of serious and nonserious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other noninterventional solicited sources, initially received from the IBD (06 Jan 2023) to 05 Jul 2024, is presented in Appendix 3. These adverse reactions are derived from the following sources: spontaneous individual case safety reports (ICSRs) including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide), and solicited non-interventional ICSRs including those from non-interventional studies. Of note, there may be slight differences in the counts in the listing relative to those in the discussion of ARIA and ICH due to follow up information received following the cutoff date for the ARIA analysis, inclusion of nonserious solicited reports in the discussion of ARIA and the separate presentation of reports of ARIA and ICH>1 cm from the Japanese postmarketing setting.

Cumulatively there have been 886 reports received. The majority of the reports received are non-serious and consistent with either known adverse drug reactions for lecanemab (e.g., ARIA, infusion reaction, headache) or events that are common in the population receiving lecanemab.

There have been 14 reports of ischemic cerebrovascular events. A review of the reports revealed that the majority of reports were found at the time of the scheduled safety MRIs, were small and asymptomatic, and were classified as serious by the company as the Eisai important medical event list includes “cerebrovascular accident”. Cerebrovascular ischemic events are relatively common in the population being treated and rates of cerebrovascular ischemic events were similar between LEC10-BW and PBO in Study 301. Considering the risk of cerebral ischemic events in this population and the increased likelihood of incidental findings given the increased MRI monitoring the rate of ischemic cerebrovascular events appears to be consistent with that observed clinical development programme and the population being treated.

Overall, the post-marketing safety reports received are consistent with the safety profile for lecanemab that was observed in the clinical development programme.

5.1.1.3.12. Summary of All Risk Minimisation Measures/Additional Pharmacovigilance Activities

The content contained in this section are new for the re-examination procedure.

The Applicant acknowledges that the CHMP seeks further assurance regarding the monitoring and management of ARIA-E, -H and ICH>1 cm in clinical practice and have proposed detailed routine risk communication, risk minimisation measures and addition pharmacovigilance activities during the MAA procedure (educational material: response to 1st D180 Question 90 and drug utilisation study: response to 2nd D180 Question 37). An overview of these measures is provided in Table 88.

In addition to previously agreed activities, the following additional activities are proposed by the applicant as part of this re-examination procedure:

- SmPC Section 4.1: Updated indication "Lecanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (early Alzheimer's disease) in adult patients that are APOE4 ("ApoE ε4") heterozygotes or noncarriers with confirmed amyloid pathology."
- SmPC Section 4.2: Addition of "with timely access to MRI" to the following statement "Treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease in centres with timely access to MRI."
- SmPC Section 4.4: Addition of "Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with LEQEMBI."
- SmPC Section 4.8: Addition of "Intracerebral Haemorrhage in the Indicated Population The incidence of intracerebral haemorrhage was 0.3% (1/286) of patients on lecanemab with a concomitant antithrombotic medication at the time of the event compared to 0.7% (3/450) of patients who did not. Patients taking lecanemab with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral haemorrhage of 1.5% (1/68 patients) compared to no patients on placebo."
- PASS to further characterise ARIA-E, -H and ICH>1 cm, effectiveness of RMMs and drug utilisation.

Table 88. Risk minimisation measures and additional pharmacovigilance

		Current Risk Minimisation Measures		
Safety Concern	**Brief Summary of Study 301 Core Data (Noncarrier and Heterozygous *APOE4* Population)**	**SmPC**	**HCP Guide, Checklist and Patient Card**	**Post-Authorisation Activity**
Monitoring for ARIA	*Symptomatic ARIA overall* LEC10-BW: 2.1% (16/757) PBO: 0.1% (1/764) *Symptomatic ARIA-E* LEC10-BW: 1.6% (12/757) PBO: 0% (0/764) *Symptomatic ARIA-H* LEC10-BW: 0.8% (6/757) PBO: 0.1% (1/764)	- Treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease in centres with timely access to MRI - Baseline MRI within 6 months for pre-existing ARIA - MRIs prior to 5th 7th and 14th infusions - Proposed MRI schedule designed to capture ~92% of ARIA-E cases - Periodic monitoring with MRIs and enhanced clinical vigilance during 1st 14 weeks - If symptoms suggestive of ARIA are present, clinical evaluation and MRI	- HCP Guide and Checklist reinforces the MRI schedule	- PASS conducted within cohorts of European lecanemab users treated in routine clinical care (utilizing databases of electronic health records) is proposed to assess: - Drug utilisation - Effectiveness of RMMs (HCP educational material) - Post marketing rates of ARIA-E, -H and ICH>1 cm - ARIA awareness and educational materials including: - ARIA detection and management for neuroradiologists - Applicant-led education meetings - Partnering with national radiology societies to increase awareness of ARIA - Suspected ARIA follow up questionnaire to monitor the nature of ARIA postmarketing
Management of ARIA		- *APOE4* genetic testing recommended to inform of risk - Suspend dosing with MRI follow-up for: - Symptomatic ARIA - Radiographically moderate ARIA - Radiographically severe ARIA - Discontinue dosing for: - Second occurrence of symptomatic ARIA-E - Second occurrence of radiographically moderate ARIA-E	- HCP Guide and Checklist reinforces ARIA management - Patient Alert Card recommends contacting HCP in the event of an ARIA symptom	

Table 88. Risk minimisation measures and additional pharmacovigilance

		Current Risk Minimisation Measures		
Safety Concern	**Brief Summary of Study 301 Core Data (Noncarrier and Heterozygous *APOE4* Population)**	**SmPC**	**HCP Guide, Checklist and Patient Card**	**Post-Authorisation Activity**
		- Second occurrence of radiographically severe ARIA - ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke.		
Monitoring for ICH>1 cm	LEC10-BW: 0.5% (4/764) (0.0040 per patient year) PBO: 0.3% (2/764) (0.0019 per patient year)	- Treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease in centres with timely access to MRI - Guidance on routine monitoring	- HCP Guide and Checklist reinforces the ARIA management	
Management of ICH>1 cm		- Suspend dosing - Permanently discontinue lecanemab at 1st occurrence - Special warning for concomitant anticoagulants and thrombolytic use - Contraindication for MRI findings suggestive of severe CAA	- HCP Guide and Checklist reinforces caution with thrombolytic agent	
Seizure as a symptom of ARIA	LEC10-BW: 1/757 (0.1%) (0.0010 per patient-year of exposure) PBO: 1/764 (0.1%) (0.0010 per patient-year of exposure)	- Special warning identifies seizure as rare ARIA symptom	- HCP Guide notes serious and life-threatening events, including seizures and status epilepticus, can rarely occur	
Acceleration of disease progression due to ARIA induced brain atrophy	Data from Study 301 Core and OLE indicates that ARIA does not adversely impact efficacy and is not associated with accelerated long-term progression. However, there is insufficient knowledge to determine whether the safety	- Statement that brain volume loss relative to placebo was observed with anti-βamyloid antibodies, but clinical consequences unknown		- "Acceleration of disease progression due to ARIA induced brain atrophy" identified as important potential risk in the RMP

Table 88. Risk minimisation measures and additional pharmacovigilance

		Current Risk Minimisation Measures		
Safety Concern	**Brief Summary of Study 301 Core Data (Noncarrier and Heterozygous *APOE4* Population)**	**SmPC**	**HCP Guide, Checklist and Patient Card**	**Post-Authorisation Activity**
	profile that will be observed over an even greater period of time differs from that characterised so far, thus further evaluation is needed.			- Ongoing Study 301 OLE Phase and Study 303 proposed as measures to provide data to further characterize the risk

ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities-oedema; ARIA-H = amyloid-related imaging abnormalities-haemorrhage; CAA = cerebral amyloid angiopathy, HCP = health care provider; LEC10-BW=lecanemab 10 mg/kg biweekly; ICH>1 cm = intracerebral haemorrhage larger than 1 cm in greatest diameter, MRI = magnetic resonance imaging; OLE = Open-label Extension; PBO = placebo; RMP= risk management plan; SmPC = summary of product characteristics

Healthcare Professional Guide and Checklist

Healthcare Professional Guide

Physicians who prescribe lecanemab will be educated on the associated risks to aid prescribers in appropriate patient selection and ensure routine follow-up is arranged. Prescribers may not be familiar with ARIA-E, -H and ICH>1 cm, and it is important that they are provided with material on the management of these events through MRI monitoring, radiographic severity criteria and treatment recommendations in clinical practice.

The HCP Guide will inform prescribing physicians of the following:

- Information on ARIA, including what it is, incidence and symptoms (ARIA-E and ARIA-H (microhaemorrhages and superficial siderosis).
- ICH>1 cm in diameter including what it is, incidence, and use of concomitant anticoagulant medication.
- How to identify and manage ARIA and ICH>1 cm in diameter through MRI monitoring, radiographic severity criteria, and the treatment recommendations.

Healthcare Professional Checklist

To promote safe use of lecanemab in conformance with the SmPC, a checklist outlining key aspects of the SmPC has been created and will be distributed to prescribing physicians. The checklist reinforces the MRI schedule through prompting the HCP to confirm booking of MRIs. Furthermore, number *APOE4* alleles is a checkbox, noting the need to discuss the incidence of ARIA across genotypes to promote awareness of the risk. Need for a baseline MRI and contraindications in line with the SmPC are also captured.

Patient Alert Card

The lecanemab Patient Alert Card focuses on providing targeted information on the potential clinical symptoms in the setting of ARIA and to reinforce the importance of seeking medical advice in a timely manner, thus promoting patient safety. The Patient Alert Card is to be used by patients to inform healthcare professionals that the patient is being treated with lecanemab.

ARIA Awareness and Educational Materials

The activities presented in this section are to aid in ensuring HCPs are familiar to the treatment management and safety of this class of products and are not formally associated with the RMP.

The real-world use of anti-amyloid therapies for AD will benefit from increased HCP awareness and preparedness for treatment management and for safety. Considerations include patient eligibility, MRI monitoring, and management of AEs such as ARIA. It is anticipated that the proposed SmPC, HCP Guide, HCP Checklist and Patient Alert Card will be all that is required to effectively communicate the necessary information to health care providers. However, it is well accepted that individuals absorb knowledge best when it is presented more frequently and in a variety of different ways.

AD specialists will likely be the lead physicians in directing the care of patients receiving lecanemab therapy, but radiologists and infusion nurses will also benefit from educational opportunities. Eisai's comprehensive educational plan aims to provide the knowledge that is appropriate for each of these types of HCPs. A range of educational opportunities will help prepare HCPs to address the needs of patients prescribed lecanemab. This plan will continuously evolve in response to our observations, the evidence and identification of unmet medical training needs/gaps.

ARIA 'Train the Trainer' Programme

The applicant has partnered with Clario, a technology company with a number of highly experienced neuroradiologists that were involved in Study 301 amongst other AD clinical trials to deliver a 'Train the Trainer' programme in order to prepare the EU market for the availability of anti-amyloid therapies. The aim of the programme is for key country radiologists to be trained on ARIA identification and subsequently be involved in Eisai organised and sponsored educational meetings at local and national level to expand the training to other neurologists.

The initial training programme involved approximately 30 radiologists from the early launch markets (i.e., Germany, Austria, France and Spain). An additional training programme is scheduled for late 2024 for later launch markets.

The programme covered CAA (overview, pattern of progression, diagnosis, MRI features), ARIA (overview and hypothesised pathophysiology), ARIA-E, -H and concurrent ARIA (characteristics, subtypes, example MRIs, risk factors, baseline imaging, monitoring, severity grading, detection and potential imaging misinterpretations), MRI protocols and several case studies.

Eisai-Developed Medical Education Content

ARIA and AD training materials have been developed and are in use in the US. These materials will be utilised in the EU and will be included on local Eisai websites following localisation (including translation if relevant) after lecanemab launch.

These materials cover relevant topics such as general AD background, subtypes of ARIA, severity grading, and differential diagnosis:

- ARIA for Neurologists
- ARIA for Radiologists
- Mechanism of Disease in Alzheimer's
- Early AD Patient Journey and Diagnosis
- Fluid and imaging Biomarkers in Alzheimer's Disease
- Case study of Mild Cognitive Impairment due to Alzheimer's Disease

Unbranded infographics for HCPs will also be available covering:

- Introduction to ARIA
- ARIA Diagnosis for the Radiologist & Neurologist
- ARIA MRI Examples and Severity Grading
- ARIA Differential Diagnosis
- Health-care Provider Discussion Guide on ARIA (to be developed following SmPC finalisation)

Instructional videos will also be available on ARIA (pathophysiology, identification, severity grading and case studies).

External-Developed Medical Education Content

The Applicant will provide a grant to an independent initiative from University College London (UCL) on ARIA education. UCL are planning to develop a European educational website – www.ariaeducation.eu - in collaboration with academics, medics, and professional societies such as European Society of

Neuroradiology and the European Academy of Neurology. The website content will focus on ARIA detection, communication, and management.

5.1.1.3.13. Post Authorisation Safety Study to Further Characterise ARIA-E, -H and ICH>1 cm, Effectiveness of Risk Minimisation Measures and Drug Utilisation

The content contained in this section are new for the re-examination procedure.

As described in response to 2nd List of D180 question 37, the applicant proposed a study to evaluate compliance and effectiveness of the HCP educational material, however the issue was considered as 'not resolved'. The Applicant understands the interest in obtaining additional EU specific data on drug utilisation and the effectiveness of the RMMs.

The Applicant is therefore proposing a new observational single-arm study conducted within cohorts of European lecanemab users treated in routine clinical care using 3 to 4 European secondary databases (utilizing databases of electronic health records). The objectives of this study will include:

- Quantify the incidence of known adverse reactions (including though not necessarily limited to ARIA-E, -H, and ICH>1 cm), characterise the severity of these adverse events in real world use, and evaluate the association between these adverse reactions and relevant covariates including but not limited to *APOE4* genotypes and concomitant antithrombotic therapy (including antiplatelet therapy, anticoagulant therapy, and thrombolytic therapy).
- Characterise the Drug Utilisation and assess the effectiveness of routine and additional RMMs, HCP education material.

- - This objective will be met by describing the population administered lecanemab, including baseline demographics, diagnosis of AD, baseline MRI findings, concomitant use of anticoagulants and antiplatelets, monitoring for ARIA, and any holding or discontinuation of lecanemab for ARIA or ICH>1 cm.

The incidence of known adverse reactions will be compared to an appropriate comparator, which is proposed as the incidence rates in the approved SmPC.

Information from this study will be submitted at timepoints aligned with the PSUR cycle.

5.1.1.3.14. Safety Conclusion

Risk factors for ARIA-E, -H, and ICH>1 cm in natural history studies (without anti-amyloid therapies), PBO, or anti-amyloid therapies, are CAA (including evidence of prior microhaemorrhage and superficial siderosis) and an increasing number of *APOE4* alleles. The Applicant has proposed excluding homozygous *APOE4* carriers from the indicated population to help address this risk.

The risks associated with LEC10-BW-treatment have been well characterised in the lecanemab development programme. Notably, ARIA events are detectable, and the applicant has proposed a number of activities to support HCPs in the monitoring and appropriate patient management if these events occur.

Pharmacovigilance activities including a follow up questionnaire to be used by HCPs when reporting postmarketing ARIA-E, -H, and ICH>1 cm events are proposed to support the characterisation of these events, with this data to be reported in PSURs. A PASS to further characterise ARIA-E, -H and ICH>1 cm, effectiveness of RMMs, and drug utilisation is also proposed by the applicant.

Collected postmarketing data is consistent with the safety profile observed in Study 301. In the countries where lecanemab is approved, health systems, academic practices, and private practices are implementing workflows to ensure the application of the label instructions.

The applicant recognises that in rare circumstances, there are symptomatic ARIA events with lecanemab, which can be serious. It is important to note that whilst these rare symptomatic events do occur, the vast majority of ARIA are asymptomatic or resolve without symptoms or clinical sequalae and hence have minimal impact on a patient's ability to continue LEC10-BW treatment.

5.1.1.4. Changes on Clinical Outcome Measures in Study 301 Show That Lecanemab slows the progression of Alzheimer's Disease and Maintains Patients' independence for Longer

5.1.1.4.1. Efficacy Executive Summary

The efficacy section is structured as follows:

- Overview of what a change on each scale represents to individual patients in terms of cognitive and functional abilities. How changes in scales translate to established stages of AD, and a summary of group-level mean changes at 18 months in Study 301 Core (Section 5.1.1.4.2. through 5.1.1.4.4.).
- Interpretation and discussion of how the group-level mean changes for each scale translate to a reduction in risk of progression to the next stage of disease (Section 0) and impact on health-related quality of life outcomes (Section 5.1.1.4.7.).
- Additional efficacy data beyond 18 months (including 36 months CDR-SB within the context of a historical cohort defined *a priori* to Study 301 [Section 5.1.1.4.9.], subgroups [Section 0].

Lecanemab was developed to slow the progression of AD in patients who are at the earliest symptomatic stages. There is a pharmacological rationale to intervene whilst patients are at the earliest symptomatic stages (MCI due to AD, mild AD).

AD is a serious, relentlessly progressive neurodegenerative disease that has a severe impact on patients, families, and healthcare systems. Established treatments are insufficient; they provide modest, temporary benefit to symptoms only and do not slow disease progression. There are no treatments approved in Europe for the predementia (MCI) stage of AD, which is the earliest symptomatic stage of AD, with impaired cognitive function. These patients are not experiencing "normal aging" as there is already cognitive impairment with amyloid plaque accumulation and neurofibrillary tangles, which result in neuronal loss and synaptic dysfunction in the brain. Patients with early AD cannot be characterised as "relatively healthy," from the perspective of brain health and daily functioning. It is important to provide treatment that maintains patients at earlier stages of AD, where they can function more independently with better health-related quality of life, thereby delaying disability from AD. This is highly meaningful to patients, care partners, and treating clinicians.

The course of symptomatic disease occurs over approximately 10 years until death. Patients at the earliest symptomatic stages experience progressive cognitive decline and functional impairment through mild cognitive impairment, and at the mild AD dementia stage lose independence; requiring assistance to perform usual daily functions (instrumental ADL) such as working (if not retired), driving, cooking, shopping, and participating in social and community activities. By the moderate dementia stage of AD, the ability to perform these activities is completely lost and assistance is needed with basic activities of daily living (bathing, dressing, toileting), a complete lack of independence.

Study 301 was a large (N=1795), global, multicentre, double-blind study to demonstrate the superiority of lecanemab versus PBO with an ongoing OLE Phase in patients with MCI due to AD or mild AD dementia (early AD) with confirmed elevated amyloid in the brain. The design of Study 301 was discussed via ad hoc requests for scientific advice and formal End of Phase 2 Meetings with the US FDA, Japan Pharmaceuticals and Medical Devices Agency (PMDA), and the EMA. At these meetings, agreement was obtained (based on PBO decline in Study 201 Core) that the design (CDR-SB as

primary endpoint), treatment duration of 18 months and patient population were appropriate to support registration of lecanemab as a treatment for early AD.

Study 301 utilised objective, globally established and validated measures of cognition and function in early AD. The scales have a wide range that is intended to reflect the entire AD continuum from MCI due to AD through to severe dementia. The population studied in Study 301 was MCI due to AD and mild AD dementia, the earliest stages of symptomatic AD; therefore, only a portion of the scale ranges are relevant for interpretation of clinical relevance in the early AD patient population.

Extensive health-related quality of life outcomes, care partner burden, and biomarkers were also assessed in Study 301.

It is agreed by the CHMP that lecanemab demonstrated a treatment effect in Study 301. For the Overall Population, LEC10-BW demonstrated a highly statistically significant 27% slowing of clinical decline on the CDR-SB after 18 months of treatment (P=0.00005). The treatment difference increased over time and was -0.45 at 18 months. In a population that excluded homozygous *APOE4* carriers "Noncarrier and Heterozygous *APOE4* Carrier Population," LEC10-BW again demonstrated a highly statistically significant 33% slowing after 18 months treatment P<0.00001. The treatment difference was -0.58 at 18 months.

Consistent, highly statistically significant slowing of decline was seen for all key secondary endpoints, which include the ADAS-Cog14 (Overall Population: 26% P=0.00065, Noncarrier and Heterozygous *APOE4* Carrier Population: 28% P=0.00052) and the ADCS-MCI-ADL (Overall Population: 37% P<0.00001, Noncarrier and Heterozygous *APOE4* Carrier Population: 39% P<0.00001).

In Study 301, the changes seen on clinical scales after 18 months translate to tangible benefits for patients and their care partners as measured by health-related quality of life outcomes. Unlike for PBO subjects, those treated with LEC10-BW had less decline in mood, self-care, finances and life as a whole. For care partners, for whom AD has an enormous detrimental impact, fewer felt as if their quality of life had suffered.

Because of the pharmacological rationale to intervene early, patients with MCI due to AD or mild AD were defined as the population in which to initiate treatment; therefore, changes from baseline in the control group will be relatively small in absolute terms and the absolute magnitude of the difference between groups will be small, even if the effect in relative terms is relevant. Assessing the importance of slowing of disease progression at the group- or subject-level is therefore dependent on how the treatment effects are quantified and characterised. As an efficient approach to statistical analysis, one approach taken by the applicant was to consider the relevance of the mean difference between LEC10-BW and PBO on (pseudo) continuous outcome scales as primary and key secondary endpoints at 18 months. However, the applicant acknowledges that absolute mean treatment differences do not provide comprehensive characterisation of effects in terms of their importance to patients. As an alternative, and in line with 2002 EMA guidance, another way to characterise effects is to assess the proportion of subjects preserved from meeting a milestone of deterioration over 18 or 36 months, or the reduction in risk of progression to next stage of disease (HR), whereby the next stages (mild AD [dependence on assistance to perform daily activities], moderate AD [no ability to perform daily activities]) reflect increasing loss of independence. These are milestones of clear clinical importance for patients.

Responder analyses evaluating the proportion of subjects worsening by meaningful amounts or thresholds of clear clinical importance are a standard approach to support assessment of the clinical relevance of treatment effect sizes. Responder analyses do this by incorporating a clinically relevant degree of disease progression at a subject-level.

These analyses showed that fewer subjects progressed to the next stage of disease with LEC10-BW, regardless of the threshold chosen. Time to progression to next stage of AD was increased with LEC10-BW, with an estimated ~30% decrease in risk of progression at any given timepoint. Another approach taken by the applicant was to quantify in time the slowing of disease progression seen with treatment.

The slowing of progression can also be translated into the time difference between treatment and PBO to reach a specified level of decline, or "time-saved" with treatment. This is a direct measure of the delay in clinical decline with treatment, representing an extension of the time patients can remain with preserved functioning. In Study 301, the PBO group reached the 18-month level of decline of the LEC10-BW group 5.3-8.0 months earlier. This reflects the time saved with treatment over 18 months:

- CDR-SB time saved relative to PBO: Overall Population approximately ~5.3 months, Noncarrier and Heterozygous *APOE4* Carrier Population ~6.1 months.
- ADAS-Cog14 time saved relative to PBO: Overall Population: ~5.9 months, Noncarrier and Heterozygous *APOE4* Carrier Population ~6.4 months.
- ADCS-MCI-ADL time saved relative to PBO: Overall Population ~7.5 months, Noncarrier and Heterozygous *APOE4* Carrier Population ~8.0 months.

In terms of expectations for treatment effects over the longer-term, LEC10-BW impacted biomarkers of amyloid, tau, and neurodegeneration, providing a biological basis for the treatment effects consistent with slowing of disease pathophysiology. Therefore, it is expected that the effects seen at 18 months will continue to expand over time as they did in the initial period of treatment and follow-up.

Data from the OLE Phase where LEC10-BW was assessed through 36 months shows the slowing of disease progression at 18 months continues to accumulate over time. The mean treatment effect continues to increase over time, translating to further time preserved in earlier stages of disease. When compared to a natural history cohort (ADNI, selected *a priori* to initiation of Study 301 to aid in the design of the study) in the OLE Phase the treatment-effect on CDR-SB continues to increase (-0.58 at 18 months, -0.86 at 36 months for the Noncarrier and Heterozygous *APOE4* Carrier Population).

Similar to the time-saved analyses performed with actual 18-month data, projections performed by the applicant using actual 36 months data for LEC10-BW, PBO and a natural history cohort to assess the amount of time to convert to the next stage of AD estimate a difference in median time to progression of disease across the target population of 12 months and that over a 5-year period, the extent to which PBO subjects deteriorate would not be reached for lecanemab treated patients for another 18 months.

Consistent with the responder/progressor analyses, health-related quality of life outcomes reinforce that the changes seen on clinical scales after 18 months translate to tangible, meaningful benefits for patients and their care partners. Long-term data show that these benefits continue to increase over time. Unlike for PBO subjects, those treated with LEC10-BW had less decline in mood, self-care, finances and life as a whole. For care partners, for whom AD has an enormous detrimental impact, fewer felt as if their quality of life had suffered.

The treatment benefits of LEC10-BW on CDR-SB and the other cognitive, functional, and health-related quality of life endpoints are comprehensive, robust, and compellingly demonstrate that treatment with LEC10-BW delays progression in early AD. This translates into maintaining patients at earlier stages of AD where they can function more independently with better health-related quality of life, thereby delaying disability from AD.

The efficacy summary that follows contains both previously submitted and new analyses, with new analyses or content identified.

5.1.1.4.2. The Primary Endpoint CDR-SB Evaluates Cognition and Function in Alzheimer's Disease

Overview of Scale and What Changes on CDR-SB Represent for an Individual Patient

The CDR (Figure 40) is a global scale of cognition and function (Hughes, et al., 1982; Morris, 1993). The tool was initially developed to measure dementia severity and covers 6 domains or "boxes": Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Scoring is determined by a clinician through a semi-structured and in-depth interview with both the patient and their study partner. The CDR yields 2 scores, the global CDR score (used for disease staging) and the CDR-SB score (used as a more sensitive and granular measure of progression):

- The global CDR score is calculated from box scores using an algorithm and ranges from 0 (no dementia), 0.5 (mild cognitive impairment), and 1 to 3 (mild, moderate and severe dementia). The global score is for disease staging (Section 0).
- The CDR-SB scores are calculated by adding the 6 category box scores and range from 0 to 18 (with higher scores indicating more impairment). This score is used as the primary basis for regulatory review and is sensitive to change over time (Section 0 and Section 0).

Of the 6 domains, 3 are for cognition (memory, orientation, judgment/problem solving) and 3 are for function (community affairs, home/hobbies, personal care). A qualified rater uses interview data and clinical judgment to assign scores for each domain ranging from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3. The personal care domain does not include the 0.5 score. Scores from each domain are summed to provide the CDR-SB value ranging from 0 to 18, with higher scores indicating greater disease severity.

In early AD, patients typically range between 0.5 and 6 (Figure 39); in Study 301 the baseline CDR-SB score was 3.2.

For each domain (Figure 41) there are distinct thresholds marking transitions from 0, unimpaired, through to 3, severely impaired. Moving from 0 to 0.5 in any of the 6 domains represents a shift from unimpaired to impaired, while a shift from 0.5 to 1.0 means a change from impaired to dependent in that domain.

Such changes are noticeable and relevant to subjects and their care partners, and the CDR, with its combination of history-taking and testing, replicates the process used in clinical practice to detect important progression milestones. Examples of impact on subjects reflected by CDR domain score changes are provided in Figure 42.

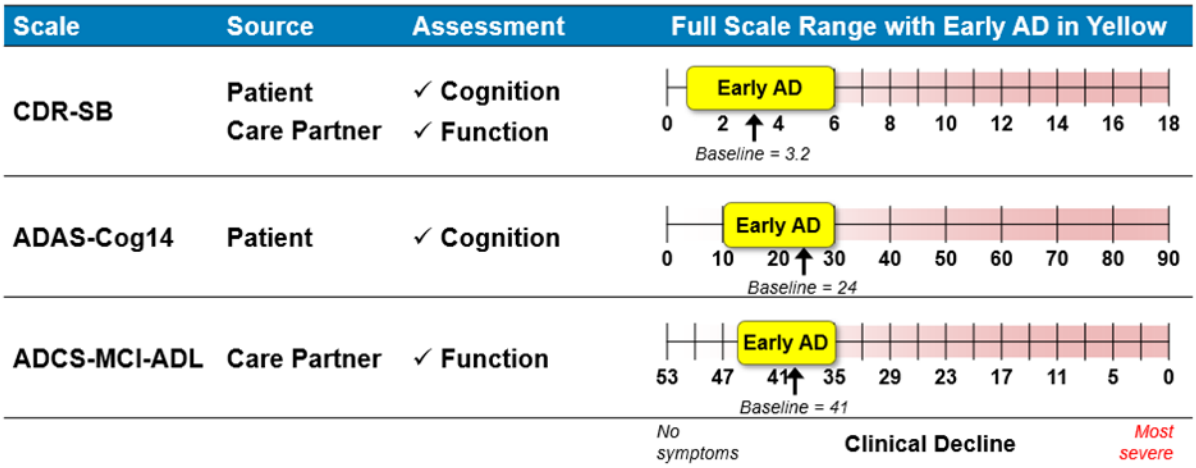


Figure 39. Study 301 established, validated and globally accepted clinical endpoints

AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14 item version, ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, CDR-SB = Clinical Dementia Rating-Sum of Boxes.

[figure omitted]

Figure 40. The CDR scale

CDR = Clinical Dementia Rating.
Source: Morris, 1997.

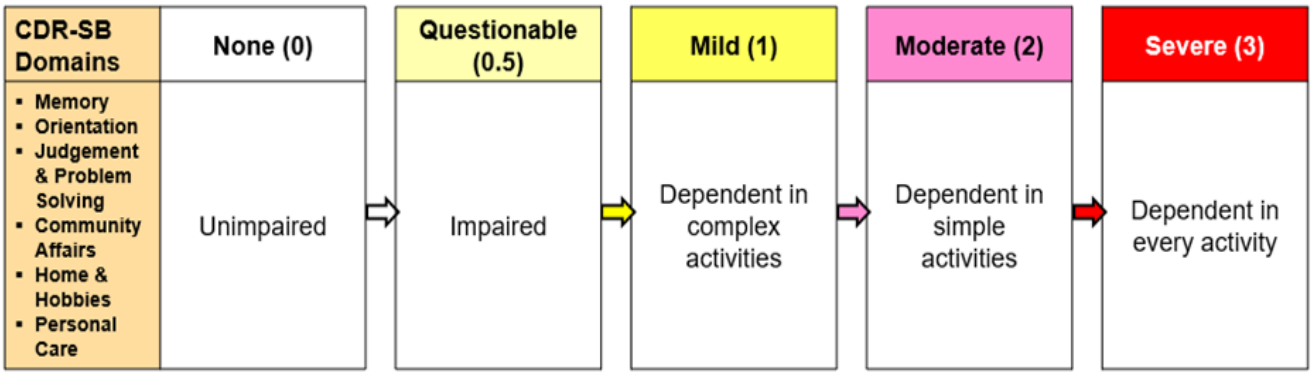


Figure 41. Each CDR-SB domain score change is meaningful to subjects

CDR-SB = Clinical Dementia Rating-Sum of Boxes.

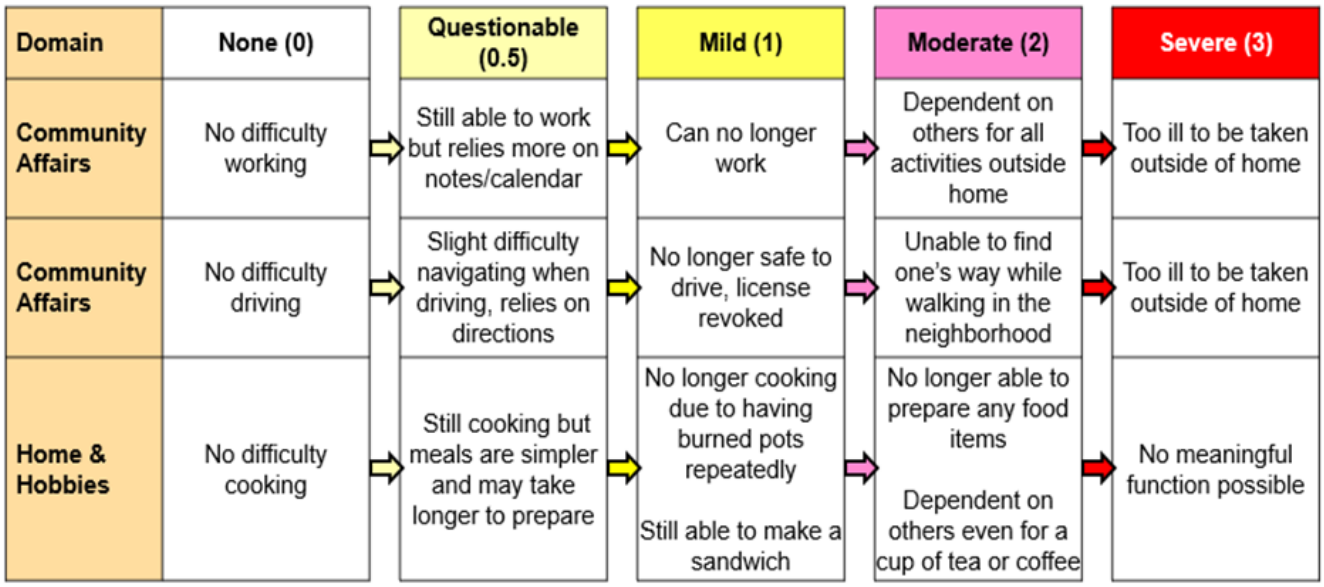


Figure 42. Examples of impact on subjects reflected by CDR domain score changes

CDR = Clinical Dementia Rating.

Study 301 Results at 18 Months for CDR-SB

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Figure 43 presents the change from baseline for CDR-SB at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Results were consistent across both populations, with statistically significant differences between PBO and LEC10-BW:

- For the Overall Population, the adjusted mean treatment difference was -0.45, 27.1% less decline with LEC10-BW compared to PBO, P=0.00005.
- For the Noncarrier and Heterozygous *APOE4* Carrier Population, the adjusted mean treatment difference was -0.58, 33.5% less decline with LEC10-BW compared to PBO, P<0.00001.

For both populations the results seen at 18 months were sustained though 36 months (Section 5.1.1.4.9.).

The effects seen at a group-level consist of clinically relevant changes at the individual level. Individuals can only deteriorate in increments of 0.5 or 1 on the CDR-SB, which represents a significant clinical change and as described in Figure 42, these changes represent noticeable and relevant change to patients and their ability to think and function. This means that the effect seen with LEC10-BW at a group-level can only arise from differences in the number of clinically relevant changes to individual patients that are experienced in each treatment group.

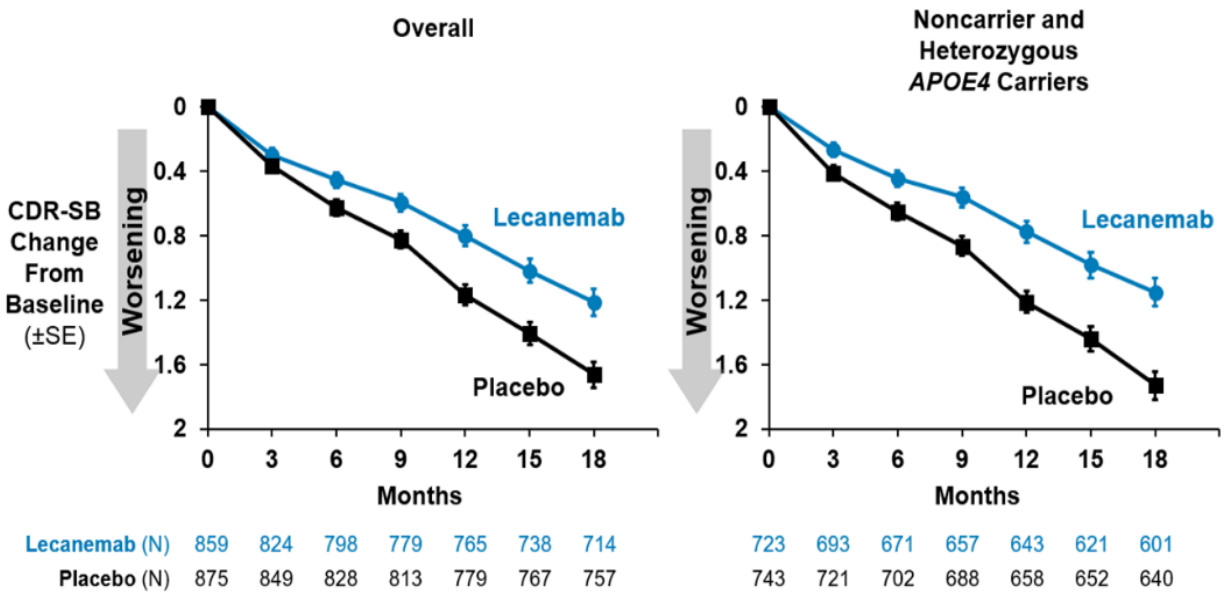


Figure 43. Adjusted mean change from baseline in CDR-SB – study 301 core (mITT)

APOE4 = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, MMRM = mixed model for repeated measures, SE = standard error, mITT = modified intent to treat.
Source: Study 301 Core CSR Table 14.2.1.1.2 and Appendix 1 Table 14.2.1.1.2nh.

Sensitivity and Supplementary Analyses

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

For CDR-SB in the Overall Population, extensive sensitivity analyses to assess various assumptions on missing data and approaches to intercurrent events were performed and described in the Study 301 Core CSR Table 8.

All observed data were included in the primary analysis, including data collected after intercurrent events (International Council for Harmonisation [ICH] E9 [R1], 2019), i.e., initiation of new AD concomitant treatment or change of AD concomitant treatment or treatment discontinuation. Analyses assessing for the impact of these intercurrent events, different approaches to assumptions on missing data, impact of ARIA events etc. are provided in the CSR. Table 89 includes the following MMRM analyses: (1) with control based multiple imputation of missing data and (2), based on all randomised subjects. The results of all plausible sensitivity analyses support the robustness of the primary analysis results.

Furthermore, tipping point analyses were conducted to assess how severe departures must be from the missing at random (MAR) assumption to overturn the conclusion of the primary analysis. The delta required to overturn the primary analysis (tipping point) was 1.5 (Study 301 Core CSR Figure 14.2.1.2.2 and Study 301 Core CSR Table 14.2.1.2.2). With delta=1.0, a statistically significant difference between PBO and LEC10-BW was still seen ($P<0.05$). A tipping point of 1.5, i.e., an assumption of 2.71 change from Baseline on CDR-SB for early discontinued subjects on LEC10-BW, implying that subjects who discontinued from study on LEC10-BW must progress far faster than PBO subjects in order to reach a nonsignificant result. The delta associated with the tipping points is not plausible, especially given overall decline of 1.66 on PBO at 18 months, hence results from the primary analysis were robust to plausible departures from MAR.

Table 89. Change from baseline in CDR-SB at 18 months – sensitivity and supplementary analyses – overall population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference	*P* value
MMRM with control-based imputation of missing data Analysis set = mITT	1.679	1.259	-0.419	(-0.640, -0.198)	<0.001
MMRM on all randomised subjects[a]. Analysis set = Randomised Set	1.659	1.225	-0.434	(-0.644, -0.224)	<0.001

CDR-SB = Clinical Dementia Rating-Sum of Boxes, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1795) are included.
Source: Appendix1 Table 14.2.1.2.52 and Study 301 Core CSR Table 14.2.1.2.24.

Table 90 provides sensitivity and supplementary analyses for the Noncarrier and Heterozygous *APOE4* Carrier Population.

Table 90. Change from baseline in CDR-SB at 18 months – sensitivity and supplementary analyses – noncarrier and heterozygous APOE4 carrier population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference	*P* value
MMRM with control-based imputation of missing data Analysis set = mITT	1.748	1.209	-0.538	(-0.774, -0.303)	<0.001
MMRM on all randomised subjects[a]. Analysis set = Randomised Set	1.722	1.168	-0.554	(-0.777, -0.331)	<0.001

CDR-SB = Clinical Dementia Rating-Sum of Boxes, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1521) are included.
Source: Appendix1 Table 14.2.1.2.52.7e and Table 14.2.1.2.24nh.

5.1.1.4.3. Key Secondary Endpoint ADAS-Cog14 Measures Cognition in Alzheimer's Disease

Overview of Scale and What Changes on ADAS-Cog14 Represent for an Individual Patient

The ADAS is a rater-administered instrument that was designed to assess the severity of dysfunction in the cognitive and noncognitive behaviours characteristic of persons with AD (Rosen, et al., 1984). The cognitive subscale of the ADAS, the ADAS-Cog14, consists of 14 distinct assessments of cognitive function that are the most typically impaired in AD: orientation, executive function verbal memory, language, praxis (learned motor activity), delayed free recall, digit cancellation, and maze-completion.

In early AD, patients typically range between 10 and 30 (Figure 39), indicative of the heterogeneity, pervasiveness, and breadth of the cognitive deficits experienced by patients; in Study 301 the baseline ADAS-Cog14 score was 24.

Study 301 Results at 18 Months for ADAS-Cog14

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Figure 44 presents the change from baseline for ADAS-Cog14 at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Similar to CDR-SB, results were consistent across both populations, with statistically significant differences between PBO and LEC10-BW:

- For the Overall Population the adjusted mean treatment difference was -1.44, and 25.8% less decline with LEC10-BW compared to PBO, *P*=0.00065
- For the Noncarrier and Heterozygous *APOE4* Carrier Population -1.63, and 27.9% less decline with LEC10-BW compared to PBO, *P*=0.00052.

For both populations, the results seen at 18 months were sustained though 36 months (Section 5.1.1.4.9.).

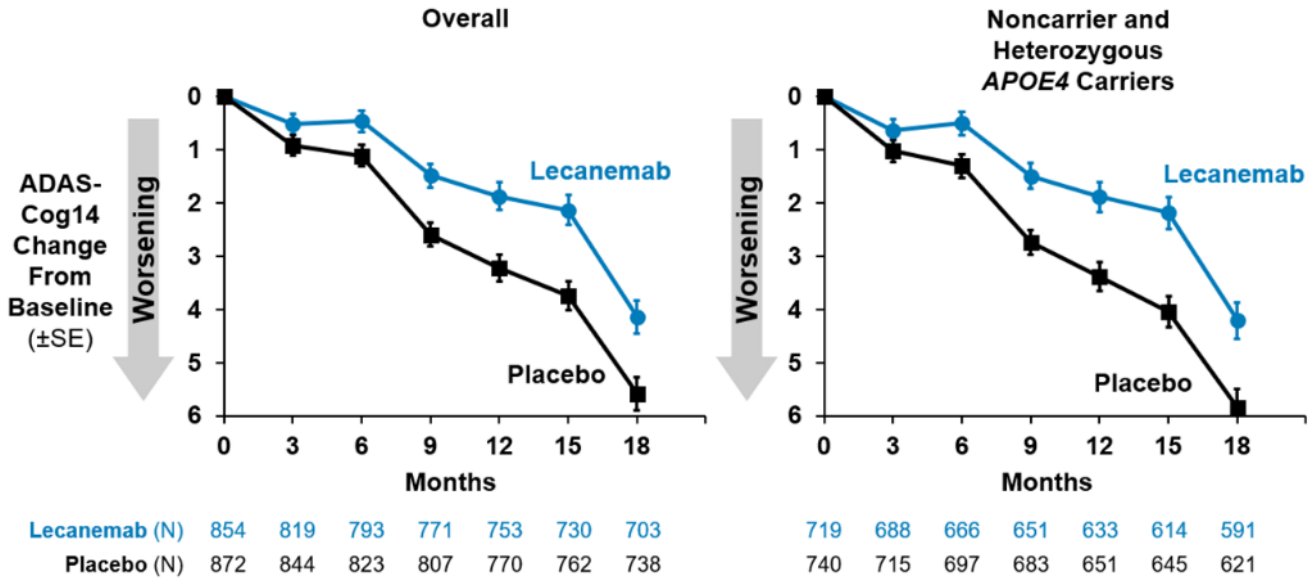


Figure 44. Adjusted mean change from baseline in ADAS-Cog14 – study 301 core (mITT)

The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit.

AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, SE = standard error, mITT = modified intent to treat.
Source: Study 301 Core CSR Table 14.2.2.2.2 and Appendix 1 Table 14.2.2.2.2nh.

Sensitivity and Supplementary Analyses

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Similar to CDR-SB, numerous sensitivity analyses were performed for ADAS-Cog14 including data collected after intercurrent events, i.e., initiation of new AD concomitant treatment or change of AD concomitant treatment or treatment discontinuation. Analyses assessing for the impact of these intercurrent events, different approaches to assumptions on missing data, impact of ARIA events, etc, are provided in the CSR (Study 301 Core CSR Section 11.4.1.2.2). Table 91 presents MMRM analyses: (1) with control based multiple imputation of missing data and (2), based on all randomised subjects. The results of all plausible sensitivity analyses support the robustness of the primary analysis results.

Furthermore, tipping point analyses were conducted to assess how severe departures must be from the MAR assumption to overturn the conclusion of the primary analysis. The delta required to overturn the main analysis (tipping point) was 4.5. With delta=3.0, a statistically significant difference between PBO and LEC10-BW was still seen ($P<0.05$). A tipping point of 4.5 implies that subjects who discontinued from study in LEC10-BW must progress faster than PBO subjects (8.64 vs 5.58) in order to reach a non-significant result. The delta associated with the tipping point was not plausible, hence results from the main analysis were robust to plausible departures from MAR.

Table 91. Change from baseline in ADAS-Cog14 at 18 months – sensitivity and supplementary analyses – overall population

Type of sensitivity or supplementary analysis	**Adjusted mean change from baseline PBO**	**Adjusted mean change from baseline LEC10-BW**	**Adjusted mean difference**	**95% CI for difference**	***P* value**
MMRM with control-based imputation. Analysis set = mITT	5.631	4.250	-1.381	(-2.216, -0.545)	0.001
MMRM on all randomised subjects[a]. Analysis set = Randomised Set	5.547	4.162	-1.385	(-2.179, -0.591)	<0.001

AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1795) are included.
Source: Appendix 1 Table 14.2.2.2.41 and Appendix 1 Table 14.2.2.2.15.

Table 92 provides sensitivity and supplementary analyses for the Noncarrier and Heterozygous *APOE4* Carrier Population that have been performed for the re-examination procedure.

Table 92. Change from baseline in ADAS-Cog14 at 18 months – sensitivity and supplementary analyses – noncarrier and heterozygous APOE4 carrier population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference	*P* value
MMRM with control-based imputation. Analysis set = mITT	5.907	4.330	-1.577	(-2.514, -0.640)	<0.001
MMRM on all randomised subjects[a]. Analysis set = Randomised Set	5.794	4.240	-1.554	(-2.436, -0.672)	<0.001

AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1521) are included. Source: Appendix 1 Table 14.2.2.2.41.7e and Appendix 1 Table 14.2.2.2.15nh.

5.1.1.4.4. Key Secondary Endpoint ADCS-MCI-ADL Measures Functional Outcomes in Alzheimer's Disease

Overview of Scale and What Changes on ADCS-MCI-ADL Represent for an Individual Patient

The ADCS-MCI-ADL is a scale developed to assess the level of daily functioning in early AD by assessing the extent to which the subject performs home and community activities (independently or requiring support). A smaller number of items address basic self-maintenance activities (basic activities of daily living), such as dressing oneself. The informant/care partner reports function observed over the previous 4 weeks.

For context, a single point change can mean a shift from performing an activity unsupervised to requiring supervision, or a shift from requiring supervision to requiring physical assistance by the care partner (Figure 45). Such changes are noticeable and relevant to subjects and their care partners.

In early AD, patients typically range between 45 and 35 (Figure 39); in Study 301 the baseline ADCS-MCI-ADL score was 41.

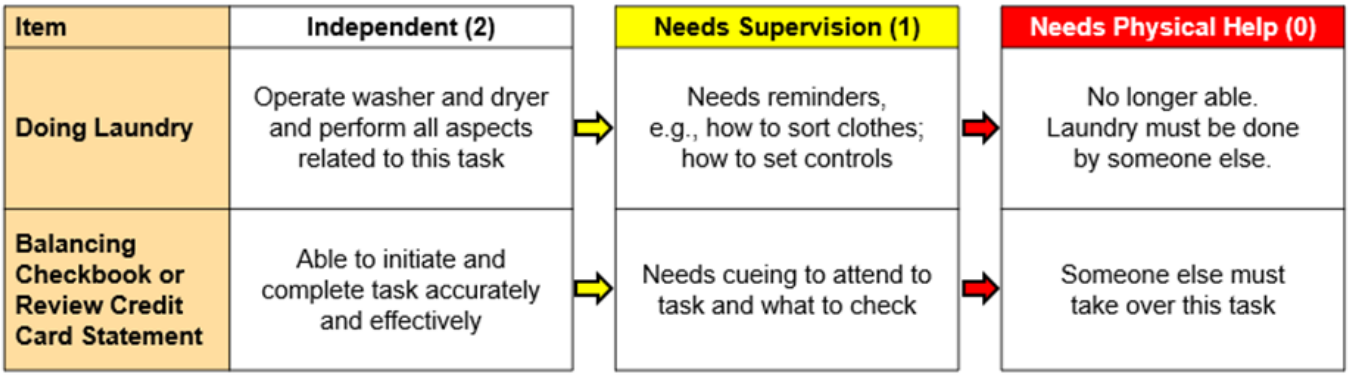


Figure 45. Examples of impact on subjects reflected by ADCS-MCI-ADL item score changes

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment.

Study 301 Results at 18 Months for ADCS-MCI-ADL

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Figure 46 presents the change from baseline for ADCS-MCI-ADL at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Again, results were consistent across both populations, with statistically significant differences between PBO and LEC10-BW:

- For the Overall Population, the adjusted mean treatment difference was 2.02, 36.6% less decline with LEC10-BW compared to PBO, $P<0.00001$.
- For the Noncarrier and Heterozygous *APOE4* Carrier Population, the adjusted mean treatment difference was 2.23, and 39.2% less decline with LEC10 BW compared to PBO, $P<0.00001$.

For both populations, the results seen at 18 months were sustained though 36 months (Section 5.1.1.4.9.).

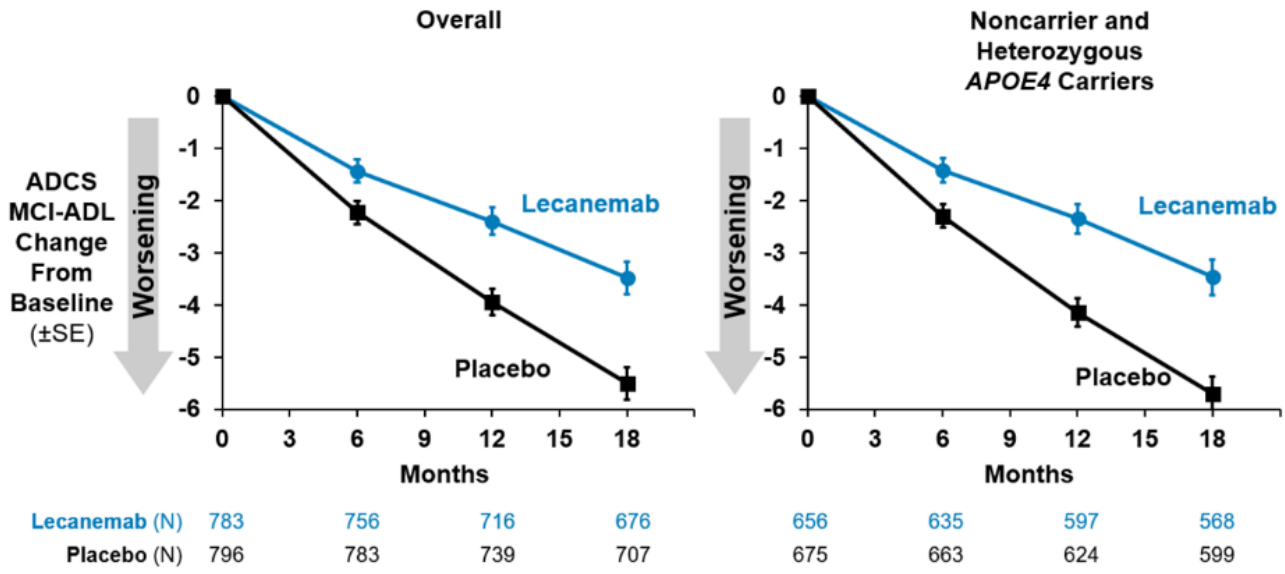


Figure 46. Adjusted mean change from baseline in ADCS-MCI-ADL – study 301 core (mITT)

The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit.
AD = Alzheimer's disease, ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment; APOE4 = apolipoprotein E4, MMRM = mixed model for repeated measures, SE = standard error, mITT = modified intent to treat.
Source: Study 301 Core CSR Table 14.2.2.4.2 and Appendix 1 Table 14.2.2.4.2nh.

Sensitivity and Supplementary Analyses

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Similar to CDR-SB, numerous sensitivity analyses were performed for ADCS-MCI-ADL including data collected after intercurrent events, i.e., initiation of new AD concomitant treatment or change of AD concomitant treatment or treatment discontinuation. Analyses assessing for the impact of these intercurrent events, different approaches to assumptions on missing data, impact of ARIA events etc. are provided in the CSR (Study 301 Core CSR Section 11.4.1.2.4). Table 93 includes the same MMRM analyses as performed for CDR-SB and ADAS-Cog14. Again, the results of all plausible sensitivity analyses support the robustness of the primary analysis results.

Furthermore, tipping point analyses were conducted to assess how severe departures must be from the MAR assumption to overturn the conclusion of the primary analysis. The delta required to overturn the main analysis (tipping point) was -12 (negative addend means worsening in ADCS-MCI-ADL). With delta = -8, a statistically significant difference between PBO and LEC10-BW was still seen ($P<0.05$). A tipping point of -12 implies that subjects who discontinued from study in LEC10-BW must progress faster than PBO subjects (-15.48 vs -5.5) in order to reach a non-significant result. The delta associated with the tipping point was not plausible, hence results from the main primary analysis were robust to plausible departures from MAR.

Table 93. Change from baseline in ADCS-MCI-ADL at 18 months – sensitivity and supplementary analyses – overall population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference	*P* value
MMRM with control-based imputation Analysis set = mITT	-5.556	-3.856	1.700	(0.882, 2.518)	<0.001
MMRM on all randomised subjects[b] Analysis set = Randomised Set	-5.366	-3.596	1.770	(1.063, 2.477)	<0.001

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1795) are included.
Source: Appendix 1 Table 14.2.2.4.41 and Appendix 1 Table 14.2.2.4.15.

Table 94 provides sensitivity and supplementary analyses for the Noncarrier and Heterozygous *APOE4* Carrier Population that have been performed for the re-examination procedure.

Table 94. Change from baseline in ADCS-MCI-ADL at 18 months – sensitivity and supplementary analyses – noncarrier and heterozygous APOE4 carrier population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference	*P* value
MMRM with control-based imputation Analysis set = mITT	-5.853	-3.839	2.014	(1.104, 2.924)	<0.001
MMRM on all randomised subjects[b] Analysis set = Randomised Set	-5.527	-3.581	1.947	(1.169, 2.724)	<0.001

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1521) are included.
Source: Appendix 1 Table 14.2.2.4.41.7e and Appendix 1 Table 14.2.2.4.15nh.

5.1.1.4.5. Interpreting the Clinical Relevance of Primary and Key Secondary Results in Accordance With EMA Guideline: Time-to-Worsening or Proportion of Subjects Worsening at Key Thresholds

LEC10-BW demonstrated slowing in disease progression of 26-37% across the primary and key secondary endpoints at the group-level in the Overall Population, and 28-39% in the Noncarrier and Heterozygous *APOE4* Carrier Population. Results remained consistent across Overall Population and Noncarrier and Heterozygous *APOE4* Population, demonstrating similar efficacy benefit across genotypes. The relevance of slowing of disease progression in these well-established and validated outcomes can be further characterised by time to progression to clinically meaningful milestones and responder/progressor analyses.

The Applicant acknowledges challenges of interpreting mean changes of slowing decline on continuous outcome scales, in particular in early stages of disease when progression rates in the absence of treatment are relatively slow in many patients. Hence, the relevance of slowing of disease progression in these well-established and validated outcomes can be further characterised by time to progression to clinically meaningful milestones and responder analyses.

The 2002 European Medicines Agency (EMA) Guideline *Points to Consider on Multiplicity Issues in Clinical Trials* acknowledges that small but statistically significant improvements in group-level outcomes in AD clinical trials can be difficult to interpret:

"In a number of applications, for example those concerned with Alzheimer's disease or epileptic disorders, it is difficult to interpret small but statistically significant improvements in the mean level of the primary variables. For this reason the term "responder" (and "non-responder") is used to express the clinical benefit of the treatment to individual patients…/…the "responder" analysis should be used in establishing the clinical relevance of the observed effect as an aid to assess efficacy and clinical safety."

The Guideline recommends the use of responder analyses to help quantify and interpret how long a disease-modifying drug can delay or halt the progression of neurodegenerative diseases such as AD. Furthermore, the 2018 *EMA Guideline on clinical investigations of medicines for the treatment of Alzheimer's disease* described the use of time to event and "time saved" analyses to interpret the effects of AD treatments. These analyses are a standard approach to establish the clinical relevance of the treatment effect and are appropriate from a clinical, statistical, and regulatory perspective to provide interpretation of the group-level treatment effect. From a clinical perspective, these types of analyses translate to the proportion of patients responding to treatment, which are easier for patients and HCPs to understand.

All multiplicity controlled prespecified analyses for Study 301 Core were highly statistically significant. As a drug effect has been established, these analyses do not need to follow Type 1 error control and per CPMP, 2002 *"can be used after statistical significance has been established on the mean level of the required primary variables"*. These analyses build the concept of clinical meaningfulness into the definition of worsening at subject level, describing the proportion of subjects who worsen by that meaningful amount.

Applying the 2002 Guideline to the results of Study 301 Core, the analyses below demonstrate that regardless of the clinically meaningful threshold or milestone, fewer subjects have clinically meaningful decline on LEC10-BW than on PBO, establishing the clinical relevance of treatment. Regardless of the threshold on each clinical scale, fewer LEC10-BW-treated subjects showed decline compared to PBO. This translates into meaningful reduction in the relative risk of decline reduction with LEC10-BW treatment at 18 months for every threshold (CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL) in the Overall Population and in the Noncarrier and Heterozygous *APOE4* Carrier Population. The higher the threshold, the greater the relative risk reduction.

(1) Lecanemab Delays Disease Progression as Measured by Global CDR Score

The Global CDR Score

AD is a serious, relentlessly progressive neurodegenerative disease. The disease stages of MCI and mild, moderate, or severe dementia (Figure 40) are used in clinical practice and also represent meaningful stages of progression in the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria for AD (Jack, et al., 2018).

The global CDR score operationalises disease staging used in the clinical setting for dementia severity; worsening of this score represents progressing to later stages of dementia, which is an event of clear clinical importance and disruption to daily life. The global CDR score represents the following stages of disease: 0 = unimpaired; 0.5 = questionable impairment (MCI); 1, 2, 3 = mild, moderate, severe dementia respectively. These are well-established stages of clinical importance, representing the syndromal categorical staging in the NIA-AA criteria (Jack, et al., 2018), and revised AD diagnostic criteria (Jack, et al., 2023). Progression to the next global CDR stage (e.g., moving from MCI to mild AD or mild AD to moderate or severe dementia) represent a clinically meaningful change since each stage (representing greater loss of function and increasing dependence) impacts a patient and their clinical management, and is therefore relevant to patients, care partners and clinicians. Hence, a drug effect that delays progression to next global CDR stage represents a relevant drug effect at the level of an individual patient. This is a direct measure of the delay in clinical decline with treatment, representing an extension of the time patients can remain with preserved functioning (i.e. independent).

Study 301 Results at 18 Months for Global CDR Score

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population and analyses by global CDR score of 0.5 and 1 in this section are new for the re-examination procedure.

The pre-specified (Overall Population) time to worsening of a global CDR score was defined as time from randomisation to the time of worsening of the global CDR score (i.e., the 1st worsening where there is an increase from Baseline in global CDR on 2 consecutive visits by at least 0.5 points for MCI subjects [baseline global CDR 0.5] and by at least 1 point for mild AD subjects [baseline global CDR 1]).

This analysis is meaningful as it represents patients moving to the next stage of AD. Such changes are noticeable and relevant to subjects and their care partners. These stages are incorporated into diagnostic criteria and regulatory guidance (FDA, 2024, Jack, 2018 and EMA, 2018):

- MCI (global CDR 0.5) – impairment in cognition, but independent on daily activities.
- Mild dementia (global CDR 1) – impairment of several cognitive domains and instrumental activities of daily living (ADLs) (driving, cooking, community activities, etc.); no longer fully independent on instrumental ADLs but independent with basic activities of daily living (bathing, dressing, toileting).
- Moderate dementia (global CDR 2) – no longer independent; dependent for instrumental ADLs, and requiring assistance for basic ADLs.
- Severe dementia (global CDR 3) – completely dependent for instrumental and basic ADLs.

Figure 47 presents time to worsening of global CDR score at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Results were consistent across both populations, with 31-34% reduced risk of progression on LEC10-BW to the next stage of disease (i.e., from MCI due to AD to mild AD or from mild AD to moderate dementia). Reduced risk of progression

with LEC10-BW was observed in both the MCI subgroup (global CDR 0.5 at baseline) and mild AD subgroup (global CDR 1 at baseline):

- For the Overall Population, the hazard ratio (HR) of disease progression on the global CDR score is 0.690 (95% CI [0.572, 0.833], *P*=0.00011). This translates to LEC10-BW reducing the risk of progression to the next stage of AD by 31%.
- When analysed by baseline global CDR score of 0.5 or 1 (Figure 48), the results remained consistent with the combined analysis:
    - Baseline global CDR score 0.5: reduced risk of progression by 32%, HR = 0.679 (95% CI [0.555, 0.831])
    - Baseline global CDR score 1: reduced risk of progression by 34%, HR = 0.655 (95% CI [0.385, 1.117])
- For the Noncarrier and Heterozygous *APOE4* Carrier Population, the HR of disease progression on the global CDR score is 0.656 (95% CI [0.534, 0.806], *P*=0.00005), reducing the risk of progression by 34% on LEC10-BW.
- When analysed by baseline global CDR score of 0.5 or 1 (Figure 48), the results remained consistent with the combined analysis:
    - Baseline global CDR score 0.5: reduced risk of progression by 34%, HR = 0.660 (95% CI [0.530, 0.822])
    - Baseline global CDR score 1: reduced risk of progression by 47%, HR = 0.528 (95% CI [0.290, 0.960])

The global CDR baseline analyses are new for the re-examination procedure.

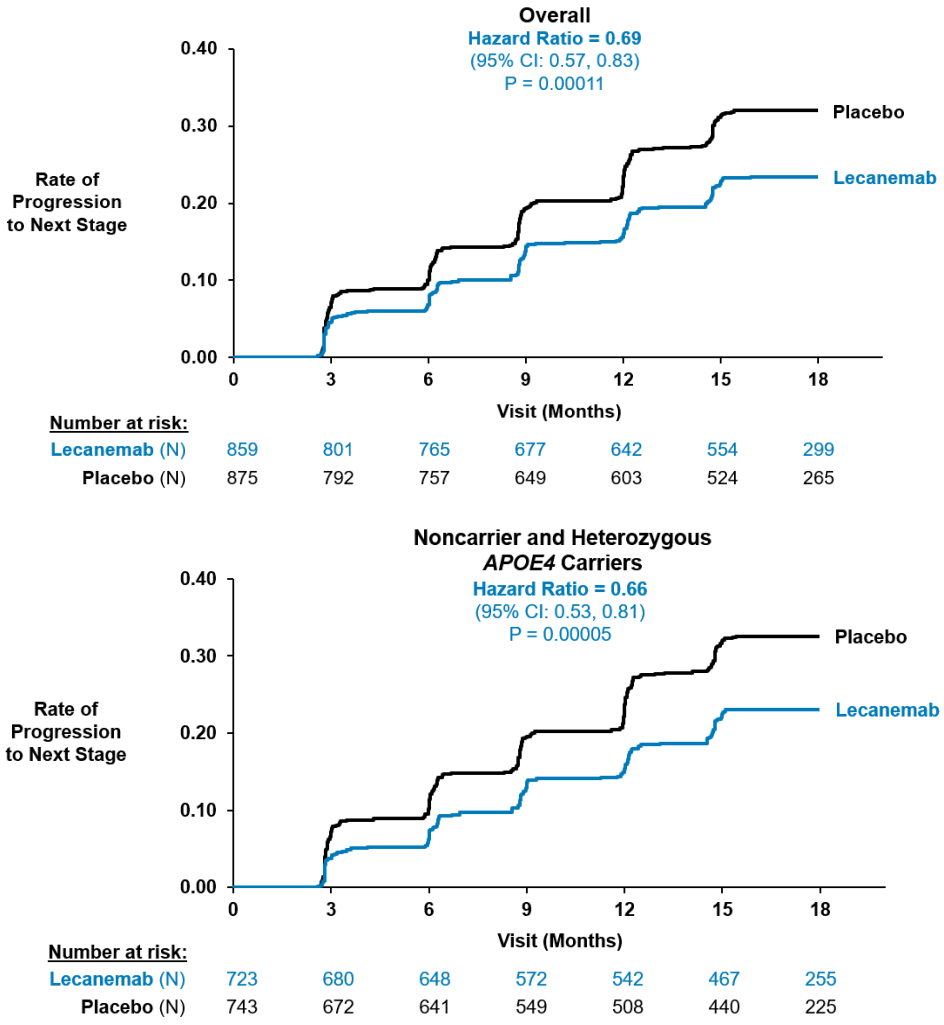


Figure 47. Kaplan–Meier curves for time to worsening of global CDR score – study 301 core (mITT)

Kaplan-Meier plot uses actual duration for time to event. Number at risk includes subjects who did not have the event nor discontinued by that visit.
APOE4 = apolipoprotein E4, CDR = Clinical Dementia Rating, mITT = modified intent to treat.
Source: Study 301 Core CSR Table 14.2.3.3.1 and Appendix 1 Table 14.2.3.3.1nh.

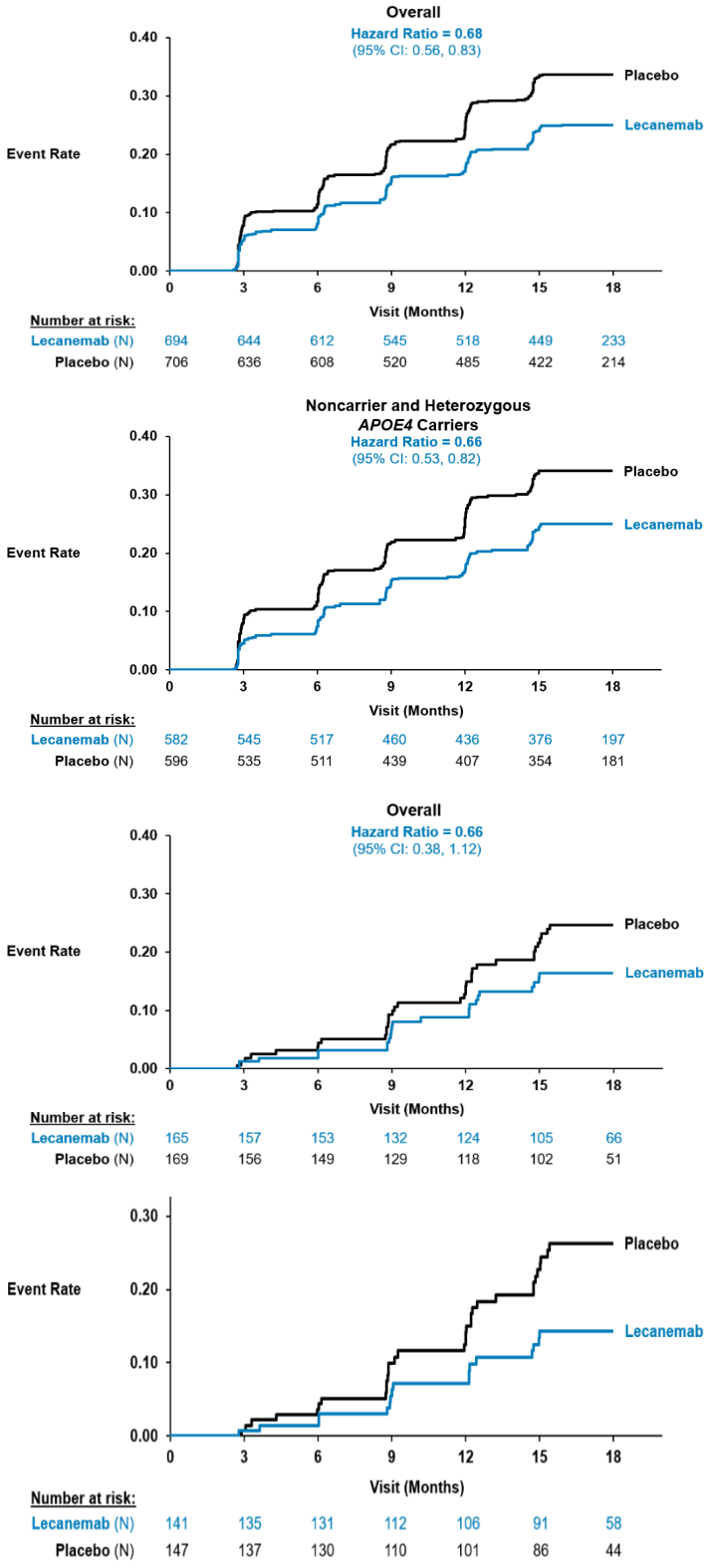


Figure 48. Kaplan–Meier curves for time to worsening of global CDR score by baseline global CDR score 0.5 (top) and 1.0 (bottom) – study 301 core (mITT)

Kaplan-Meier plot uses actual duration for time to event. Number at risk includes subjects who did not have the event nor discontinued by that visit.
APOE4 = apolipoprotein E4, CDR = Clinical Dementia Rating, mITT = modified intent to treat.
Source: Study 301 Core CSR Table 14.2.3.3.1 and Appendix 1 Table 14.2.3.3.1nh.

(2) Lecanemab Delays Disease Progression at any Threshold of CDR-SB, ADAS-Cog14 and ADCS-MCI-ADL

A complementary approach to the time to worsening on global CDR score presented in Section 0 is to assess time to worsening based on various thresholds of decline on the CDR-SB, ADAS-Cog14 and ADCS-MCI-ADL at 18 months. For each scale varying thresholds of decline were selected, with these analyses demonstrating that there is a reduction in the relative risk of clinical decline with LEC10-BW treatment for every scale and at every threshold. Across all scales, the higher the threshold selected (i.e., the greater the cognitive and function decline), the greater the relative risk reduction.

CDR-SB at 18 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

As described in Section 0, for CDR-SB, moving from **0 to 0.5** in any of the 6 domain represents a shift from unimpaired to impaired, while a shift from **0.5 to 1.0** means a change from impaired to dependent in that domain. Such changes are noticeable and relevant to subjects and their care partners.

Figure 49 presents time to event analyses (event defined as decline by 0.5 and 2.0 on CDR-SB) at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Similar to what was reported for the global CDR Score (Section 0), results were consistent across both populations with greater than 18% reduced risk of worsening by 0.5 and greater than 32% reduced risk of worsening by 2.0 on CDR-SB. There is a reduction in the relative risk of clinical decline with LEC10-BW treatment for every threshold. The higher the threshold, the greater the relative risk reduction:

- For the Overall Population:
- LEC10-BW reduced the risk of worsening by 0.5 on CDR-SB by 18%. The HR of worsening is 0.820 (95% CI [0.727, 0.924], *P*=0.00116)
- LEC10-BW reduced the risk of worsening by 2.0 on CDR-SB by 32%. The HR of worsening is 0.684 (95% CI [0.563, 0.832], *P*=0.00014)
- For the Noncarrier and Heterozygous *APOE4* Carrier Population:
- LEC10-BW reduced the risk of worsening by 0.5 on CDR-SB by 22%. The HR of worsening is 0.782 (95% CI [0.687, 0.892], *P*=0.00023)
- LEC10-BW reduced the risk of worsening by 2.0 on CDR-SB by 37%. The HR of worsening is 0.634 (95% CI [0.513, 0.784], *P*=0.00002)

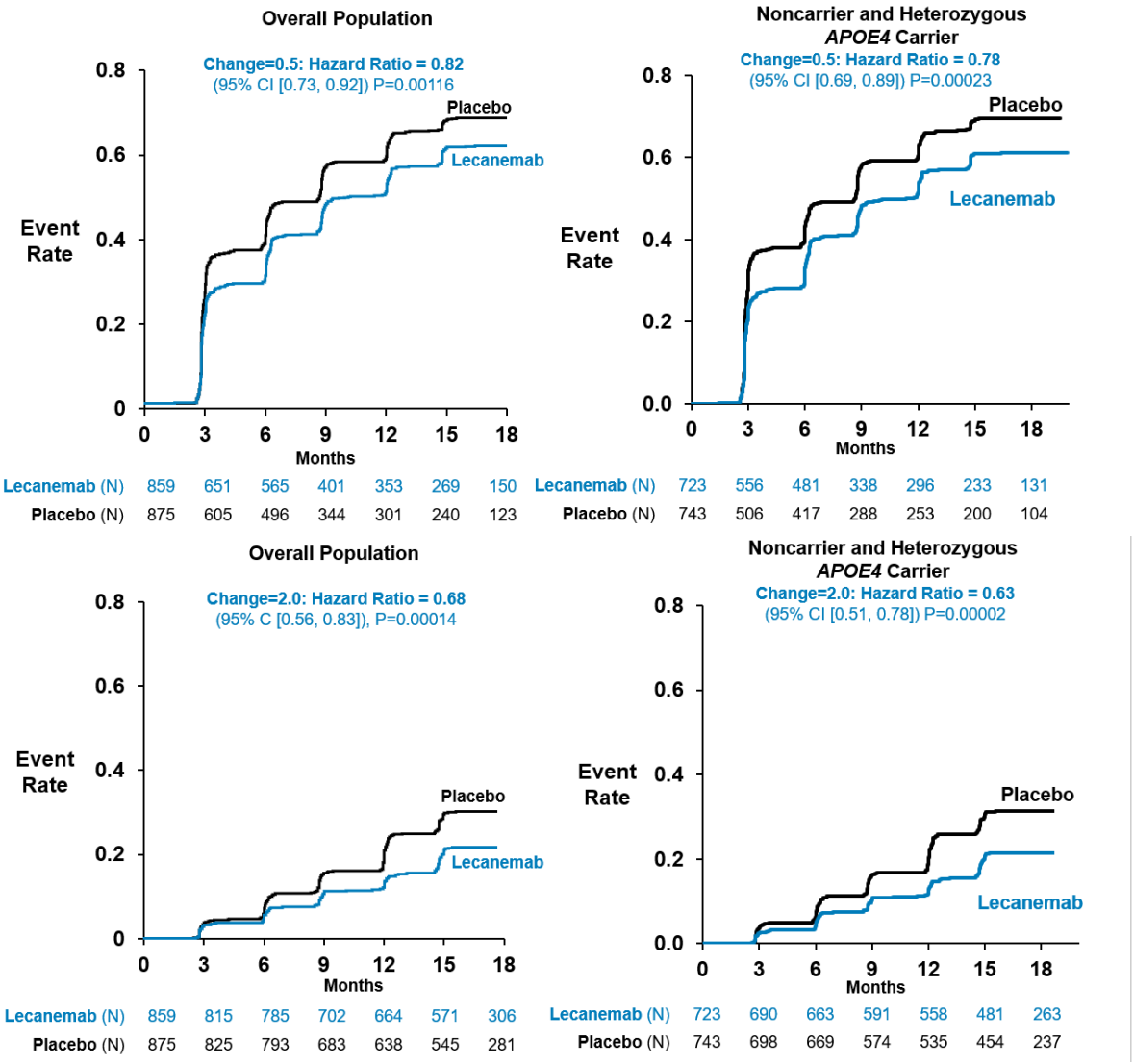


Figure 49. Kaplan–Meier curves for time to worsening of CDR-SB by CDR-SB score 0.5 (top) and 2.0 (bottom) – study 301 core (mITT)

APOE4 = apolipoprotein E4, CDR-SB = Clinical Dementia Rating-Sum of Boxes, mITT = modified intent to treat.
Source: Appendix 1 Figure 14.2.3.13.1.1nh and Appendix 1 Figure 14.2.3.13.1.2nh.

ADAS-Cog14 at 18 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

As described in Section 0, the ADAS-Cog14 involves a direct assessment of the subject on 14 cognitive items assessing memory, orientation, language, executive function, and praxis (learned motor activity).

Figure 50 presents time to event analyses (event defined as decline by 2.5, 5, and 8.0 on ADAS-Cog14) at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. The 5-point threshold represents the median PBO decline. Similar to what was reported CDR-SB, results were consistent across both populations with greater than 22% reduced risk of worsening by 2.5, greater than 16% reduced risk of worsening by 5 and greater than 27% reduced risk of worsening by 8 on ADAS-Cog14. There is a reduction in the relative risk of clinical decline with LEC10-BW treatment for every threshold:

- For the Overall Population:

- LEC10-BW reduced the risk of worsening by 2.5 on ADAS-Cog14 by 22%. The HR of worsening is 0.783 (95% CI [0.681, 0.902], *P*=0.00067)

- LEC10-BW reduced the risk of worsening by 5.0 on ADAS-Cog14 by 16%. The HR of worsening is 0.835 (95% CI [0.702, 0.994], *P*=0.04235)

- LEC10-BW reduced the risk of worsening by 8.0 on ADAS-Cog14 by 27%. The HR of worsening is 0.731 (95% CI [0.573, 0.931] *P*=0. 01119)

- For the Noncarrier and Heterozygous *APOE4* Carrier Population:

- LEC10-BW reduced the risk of worsening by 2.5 on ADAS-Cog14 by 24%. The HR of worsening is 0.763 (95% CI [0.655, 0.889], *P*=0.00052)

- LEC10-BW reduced the risk of worsening by 5.0 on ADAS-Cog14 by 20%. The HR of worsening is 0.803 (95% CI [0.667, 0.968], *P*=0.02118)

- LEC10-BW reduced the risk of worsening by 8.0 on ADAS-Cog14 by 29%. The HR of worsening is 0.711 (95% CI [0.547, 0.923] *P*=0.01056)

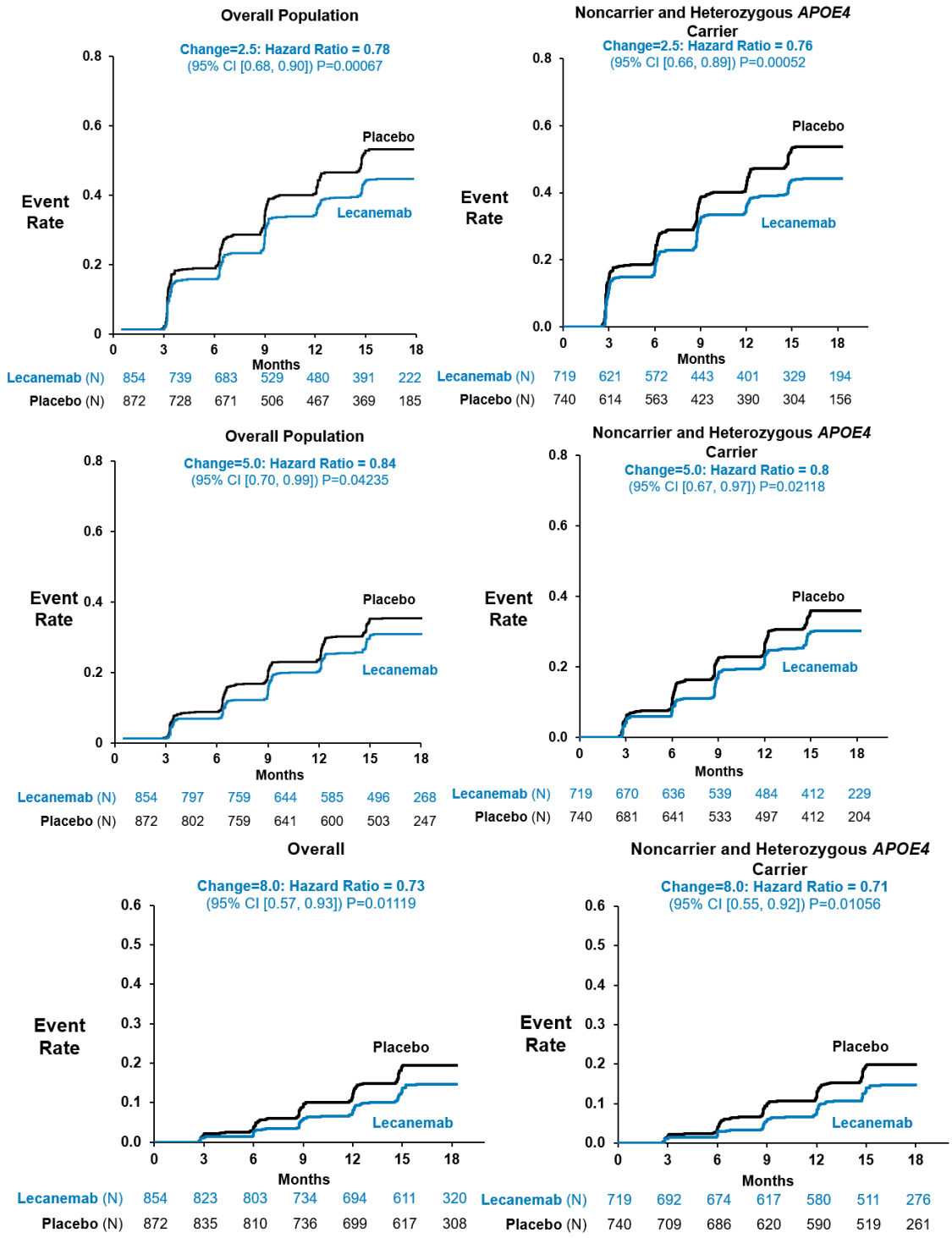


Figure 50. Kaplan–Meier curves for time to worsening of ADAS-Cog14 by ADAS-Cog14 score 2.5 (top), 5.0 (middle) and 8.0 (bottom) – study 301 core (mITT)

ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale 14-item version, *APOE4* = apolipoprotein E4, mITT = modified intent to treat.
Source: Appendix 1 Figure 14.2.3.13.2.1nh, Appendix 1 Figure 14.2.3.13.2.2nh, and Appendix 1 Figure 14.2.3.13.2.3nh.

ADCS-MCI-ADL at 18 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

As described in Section 0, for ADCS-MCI-ADL, a single point change can mean a shift from performing an activity unsupervised to requiring supervision, or a shift from requiring supervision to requiring physical assistance by the care partner.

For example, a single point change means being able to independently undertake laundry to needing reminder on sorting clothes and how to set controls, with another single point change resulting in a caregiver needing to undertake this activity. Such changes are noticeable and relevant to subjects and their care partners.

Figure 51 presents time to event analyses (event defined as decline by -3.0 and -6.0 on ADCS-MCI-ADL) at 18 months for the Overall Population and the Heterozygous *APOE4* Carrier Population. Similar to what was reported for the other scales, results were consistent across both populations with greater than 23% reduced risk of worsening by -3.0 and greater than 32% reduced risk of worsening by -6.0 on ADCS-MCI-ADL. There is a reduction in the relative risk of clinical decline with LEC10-BW treatment for every threshold. The higher the threshold, the greater the relative risk reduction:

- For the Overall Population:

- LEC10-BW reduced the risk of worsening by -3.0 on ADCS-MCI-ADL by 24%. The HR of worsening is 0.756 (95% CI [0.639, 0.895], *P*=0.00117).

- LEC10-BW reduced the risk of worsening by -6.0 on ADCS-MCI-ADL by 32%. The HR of worsening is 0.677 (95% CI [0.536, 0.854], *P*=0.00102).

- For the Noncarrier and Heterozygous *APOE4* Carrier Population:

- LEC10-BW reduced the risk of worsening by -3.0 on ADCS-MCI-ADL by 23%. The HR of worsening is 0.769 (95% CI [0.641, 0.922], *P*=0.00458).

- LEC10-BW reduced the risk of worsening by -6.0 on ADCS-MCI-ADL by 34%. The HR of worsening is 0.655 (95% CI [0.509, 0.844], *P*=0.00108).

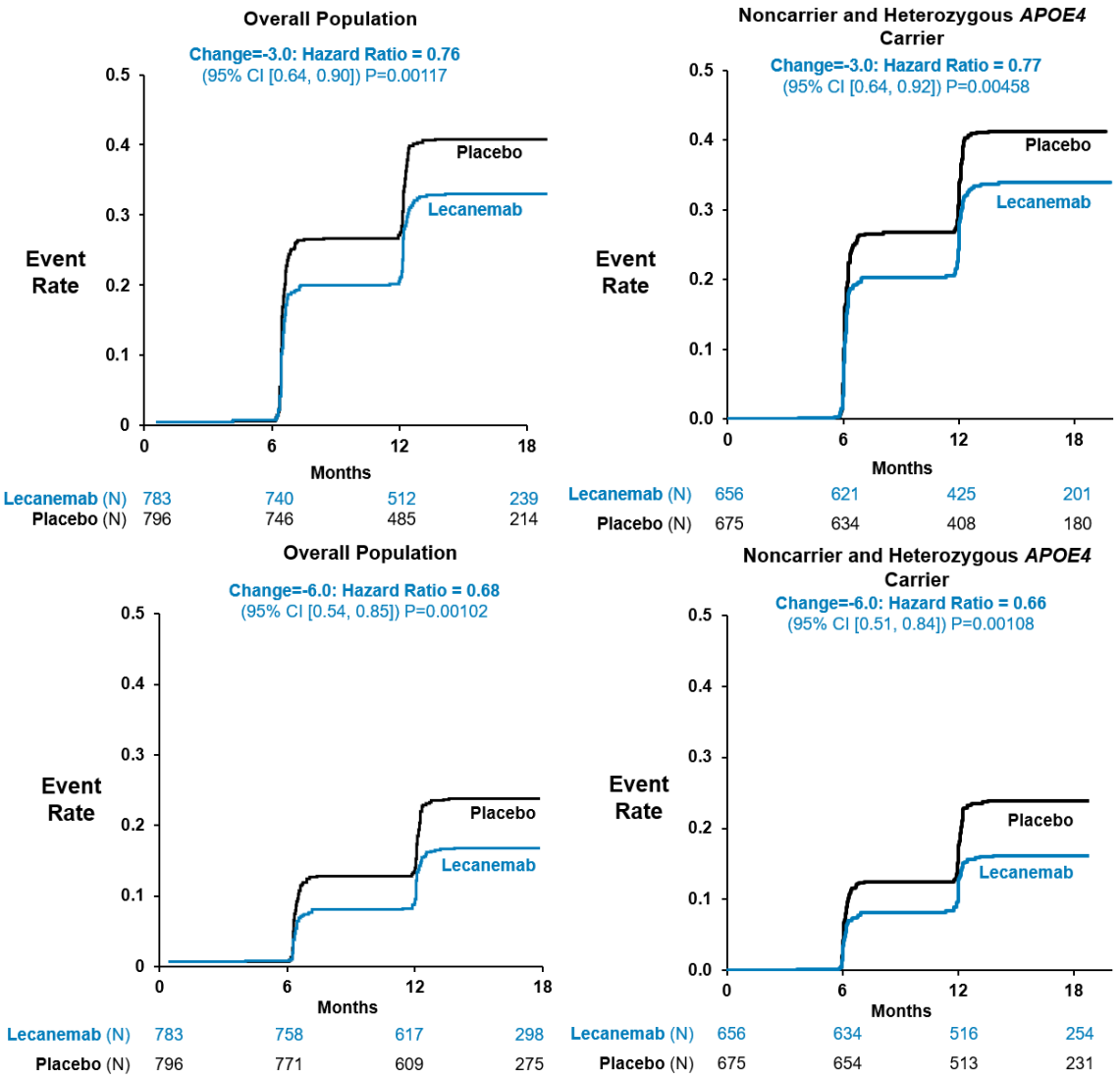


Figure 51. Kaplan–Meier curves for time to worsening of ADCS-MCI-ADL by ADCS-MCI-ADL score -3.0 (top) and -6.0 (bottom) – study 301 core (mITT)

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, *APOE4* = apolipoprotein E4, mITT = modified intent to treat.
Source: Appendix 1 Figure 14.2.3.13.3.1nh and Appendix 1 Figure 14.2.3.13.3.2nh.

(3) Progressor Analyses

To compliment the time to worsening Kaplan-Meier plots presented in Sections 0 and 0, progressor analyses to assess the proportion of subjects in PBO and LEC10-BW that progressed by increasing thresholds on the CDR-SB, ADAS-Cog14 and ADCS-MCI-ADL scales in Study 301 by 18 month were performed. These are meaningful analyses since they incorporate subject level changes into the definition. In addition, these analyses are based on a combination of observed data and a conservative control-based imputation for data that were missing was used so that a complete 18-month dataset could be used for every subject in the study.

In the following figures the x-axis represents a range of possible scale changes by 18 months of treatment with each column providing incremental thresholds of worsening. The 2 left columns show all subjects and whether they had no decline or any decline (except for ADCS-MCI-ADL with these shown in the 2 right columns). The bars represent the proportion of subjects that reached that level of decline or greater.

Consistent with other analyses intended to demonstrate the meaningfulness of the primary and secondary outcomes, there is a reduction in the relative risk of clinical decline with LEC10-BW treatment for every scale and at every threshold. Across all scales, the higher the threshold, the greater the relative risk reduction.

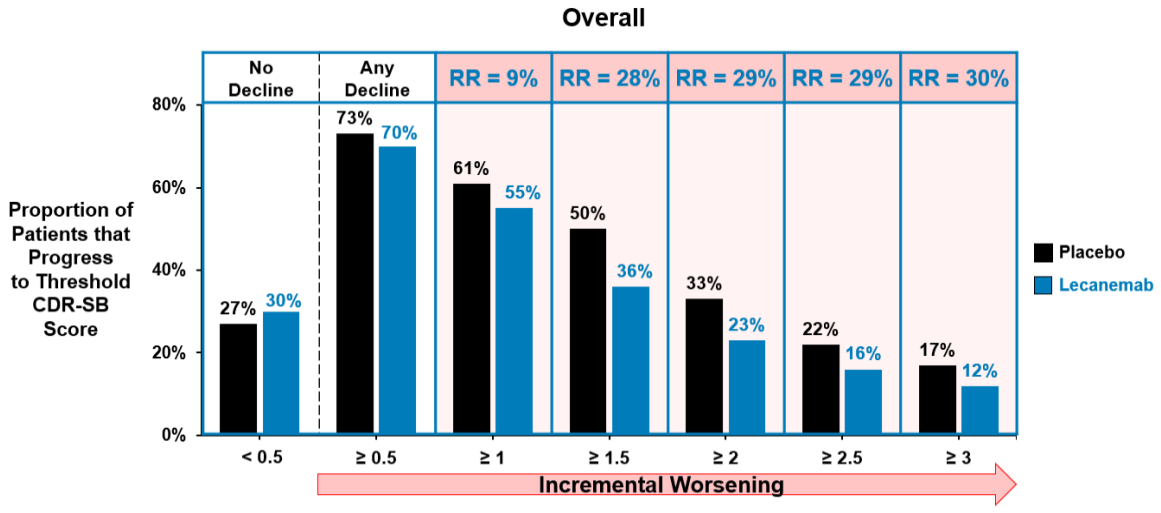
CDR-SB at 18 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Figure 52 presents progressor analyses at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population for CDR-SB. Results were consistent across both populations, with a reduction in the relative risk of cognitive and functional decline with LEC10-BW treatment for every threshold (0.5 to a 3-point worsening on CDR-SB). The higher the threshold, the greater the reduction in the relative risk.

For example, the middle column quantitates subjects that progressed by 1.5 or more on CDR-SB, since that represents the median decline for PBO. A 1.5-point decline would generally reflect a subject deteriorating in more than one cognitive or functional CDR-SB domains. At this threshold:

- For the Overall Population, 50% of PBO subjects declined compared to 36% of LEC10-BW subjects, representing a 28% reduction in relative risk.
- For the Noncarrier and Heterozygous *APOE4* Carrier Population 53% of PBO subjects declined compared to 35% of LEC10-BW subjects, representing a 34% reduction in relative risk.



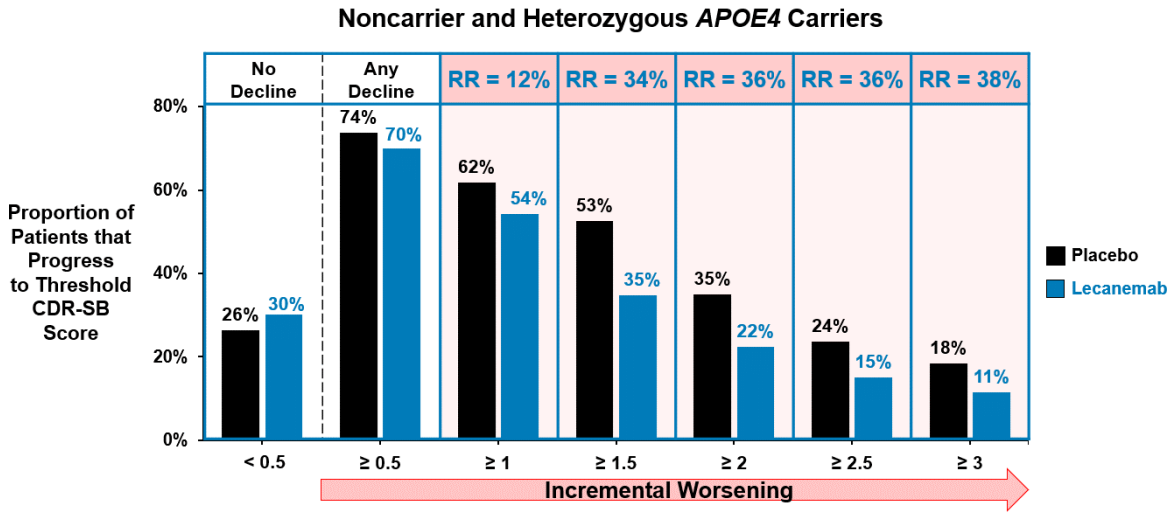


Figure 52. Progressor analyses for the proportion of subjects with cognitive and functional worsening on CDR-SB – study 301 core (ITT)

APOE4 = apolipoprotein E4, CDR-SB = Clinical Dementia Rating-Sum of Boxes, ITT = intent to treat.
Source: Appendix 1 Table 14.2.3.14.1nh.

ADAS-Cog14 at 18 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Figure 53 presents progressor analyses at 18 months for the Overall Population and the Heterozygous *APOE4* Carrier Population for ADAS-Cog14. Similar to CDR-SB, results were consistent across both populations, with a reduction in the relative risk of cognitive decline with LEC10-BW treatment (1 to a 16-point worsening on ADAS-Cog14). The higher the threshold, the greater the reduction in the relative risk.

For example, the middle column quantitates subjects that progressed by 5 or more on ADAS-Cog14, since that represents the median decline for PBO. A 5-point decline would generally reflect a subject deteriorating across multiple cognitive domains. At this threshold:

- For the Overall Population, 45% of PBO subjects declined compared to 39% of LEC10-BW subjects, representing a 14% reduction in relative risk.
- For the Noncarrier and Heterozygous *APOE4* Carrier Population 47% of PBO subjects declined compared to 40% of LEC10-BW subjects, representing a 15% reduction in relative risk.

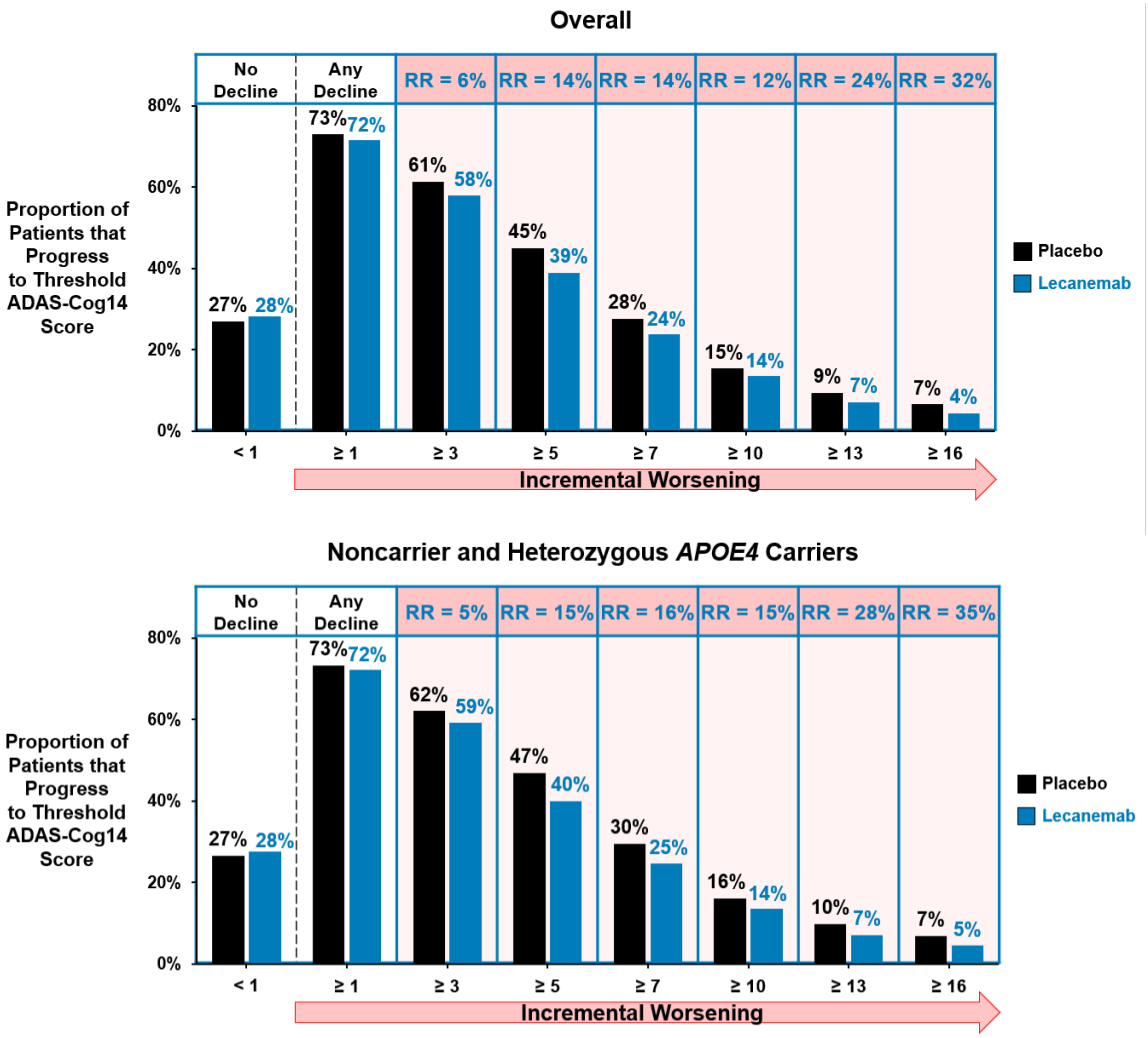


Figure 53. Progressor analyses for the proportion of subjects with cognitive worsening on ADAS-Cog14 – study 301 core (ITT)

ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale 14-item version, *APOE4* = apolipoprotein E4, ITT = intent to treat.
Source: Appendix 1 Table 14.2.3.14.2nh.

ADCS-MCI-ADL at 18 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population in this section are new for the re-examination procedure.

Figure 54 presents progressor analyses at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population for ADCS-MCI-ADL. For this scale the thresholds increase from right to left on the x-axis, because negative change is worse. The proportion with and without any decline are the right 2 columns.

As with the other scales, results were consistent across both populations, with a reduction in the relative risk of cognitive and functional decline with LEC10-BW treatment for every threshold (-1 to a -7-point worsening on ADCS-MCI-ADL). The higher the threshold, the greater the reduction in the relative risk.

For example, the middle column quantitates subjects that declined by -5 or more on ADCS-MCI-ADL, since that represents a decline close to the median decline for PBO. A -5-point decline would generally reflect a subject significantly deteriorating across multiple daily activities. At this threshold:

- For the Overall Population, 43% of PBO subjects declined compared to 28% of LEC10-BW subjects, representing a 34% reduction in relative risk.
- For the Noncarrier and Heterozygous *APOE4* Carrier Population 45% of PBO subjects declined compared to 30% of LEC10-BW subjects, representing a 34% reduction in relative risk.

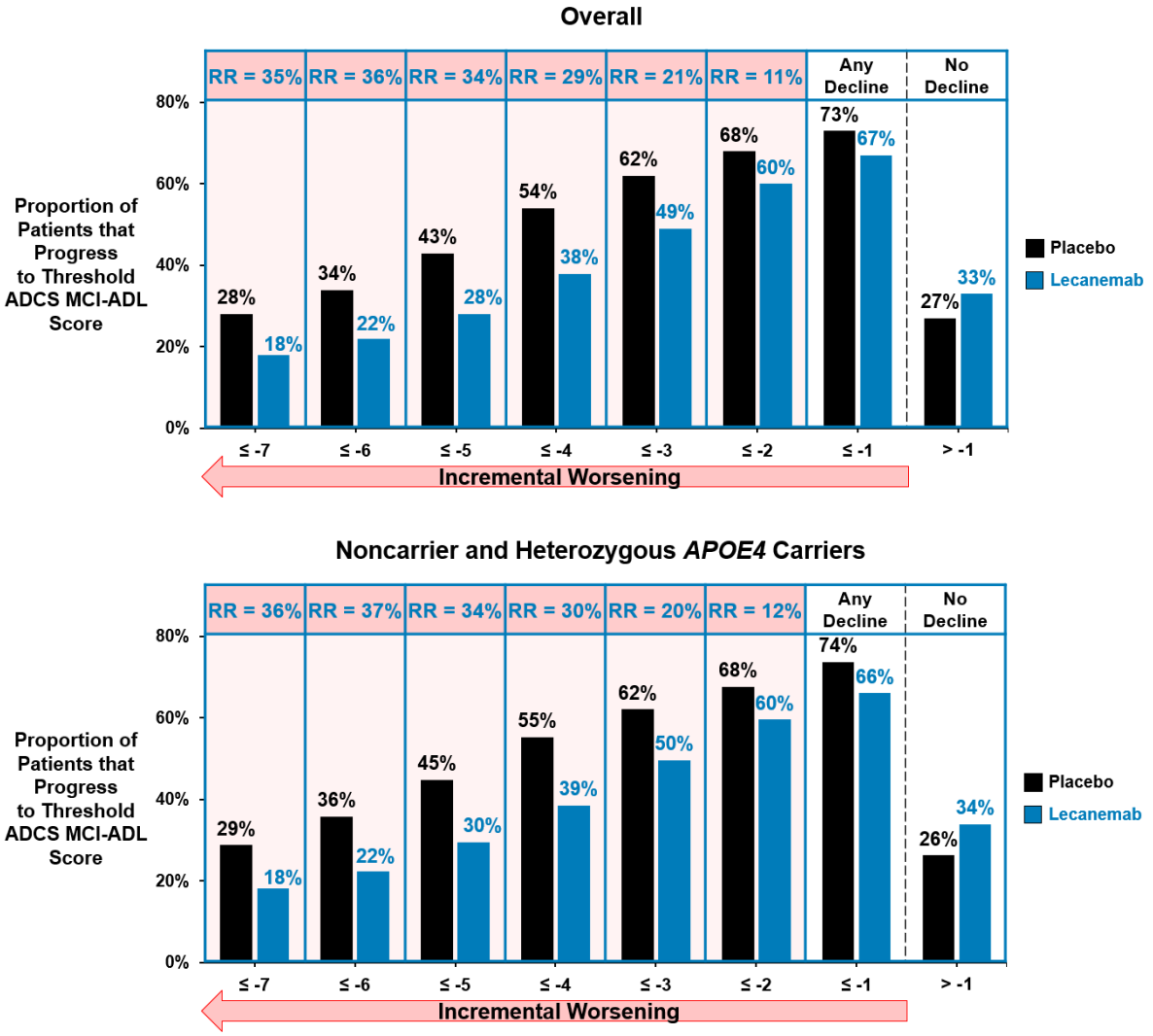


Figure 54. Progressor analyses for the proportion of subjects with functional worsening on ADCS-MCI-ADL – study 301 core (ITT)

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, *APOE4* = apolipoprotein E4, ITT = intent to treat.
Source: Appendix 1 Table 14.2.3.14.3nh.

5.1.1.4.6. Time Saved Analyses Further Support That Lecanemab Maintains Subjects at Earlier Stages of Disease for a Longer Time

Time-saved analyses represent the time a patient remains with preserved cognition and function on treatment relative to PBO or the natural history of AD Figure 55. This is a direct measure of the delay in clinical decline with treatment, representing an extension of the time patients can remain with

preserved functioning. Time saved allows patients continued independence and self-autonomy to manage basic needs (such as working [if not retired], driving, personal care [toileting, bathing], continuing intellectual interests, volunteer and social group participation).

Given the known trajectory of AD (Figure 27), the amount of time saved is expected to increase when lecanemab treatment is initiated in the earliest symptomatic stages of AD (MCI due to AD and mild AD dementia). Post hoc analyses in no/low tau and low amyloid subjects (Section 5.1.1.4.8.) provide preliminary evidence of the potential increased benefits when lecanemab is started early in the AD continuum.

Lecanemab impacts underling disease pathophysiology (biomarkers of amyloid, tau, and neurodegeneration) providing a biological basis for the treatment effects consistent with slowing of disease pathophysiology. For this reason, and as demonstrated by available 36-month data (Section 5.1.1.4.9.) and long-term projection (Section 0), 'time saved' with LEC10-BW continues to increase relative to the natural history of AD.

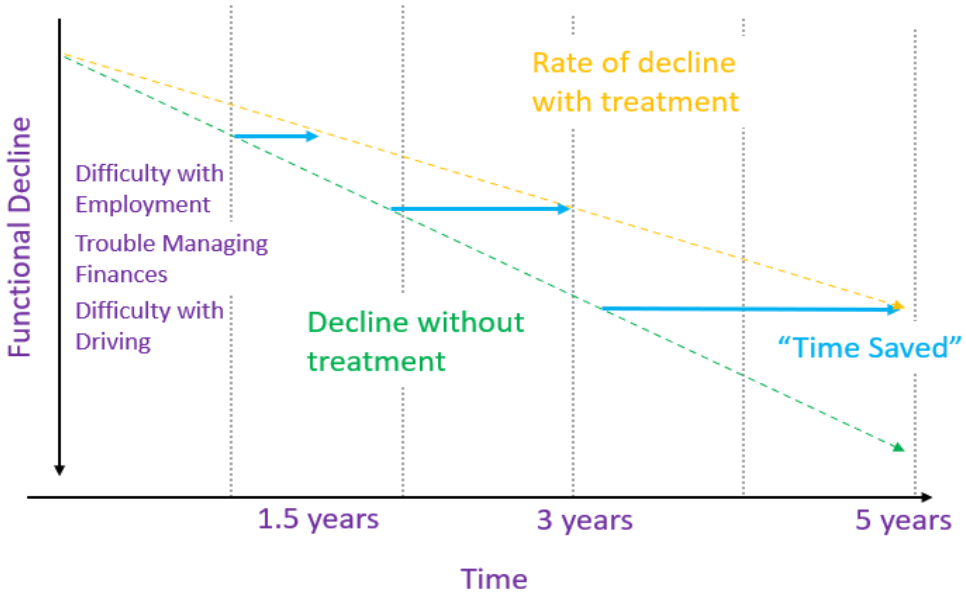


Figure 55. Depiction of the impact of disease modifying therapies on functional decline and time saved

(1) Time Saved: Slope Analyses

The slowing of cognitive and functional decline over 18 months on CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL can be interpreted as "time preserved" or "time saved due to delayed progression", whereby subjects are maintained at earlier stages of disease where they are able to function more independently, with better health-related quality of life.

CDR-SB

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population and individual genotypes in this section are new for the re-examination procedure.

Results for CDR-SB are based on a prespecified slope analysis (Overall Population):

In the Overall Population, there is increasing separation over time between PBO and LEC10-BW, with a 29.3% slowing of progression on LEC10-BW annually ([95% CI: 16.1% to 42.4%], *P*=0.00001) versus

PBO (Figure 56). The PBO group reached the 18-month level of decline of the LEC10-BW group 5.3 months earlier. These 5.3 months of time saved, representing nearly a third of the 18-month study period, is the extension of time that LEC10-BW subjects remain with preserved cognition and function relative to PBO. When projecting forward, LEC10-BW takes an additional 7.5 months to reach the clinical decline seen on PBO at 18 months (mean change in CDR-SB of 1.66).

In the Noncarrier and Heterozygous *APOE4* Carrier Population, there is increasing separation over time between PBO and LEC10-BW, with a 34.0% slowing of progression on LEC10 BW annually ([95% CI: 20.2% to 47.8%], *P*<0.00001) versus PBO (Figure 56). This separation indicates that cognition and function as assessed by CDR-SB is preserved by approximately 6.1 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 9.3 months to reach the clinical decline seen on PBO at 18 months (mean change in CDR-SB of 1.73).

A similar approach was described via the backward projection to placebo (BPP) method and additional time needed to reach PBO decline relative to treatment progression (ATNRP-T) in Wang, et al. (2024).

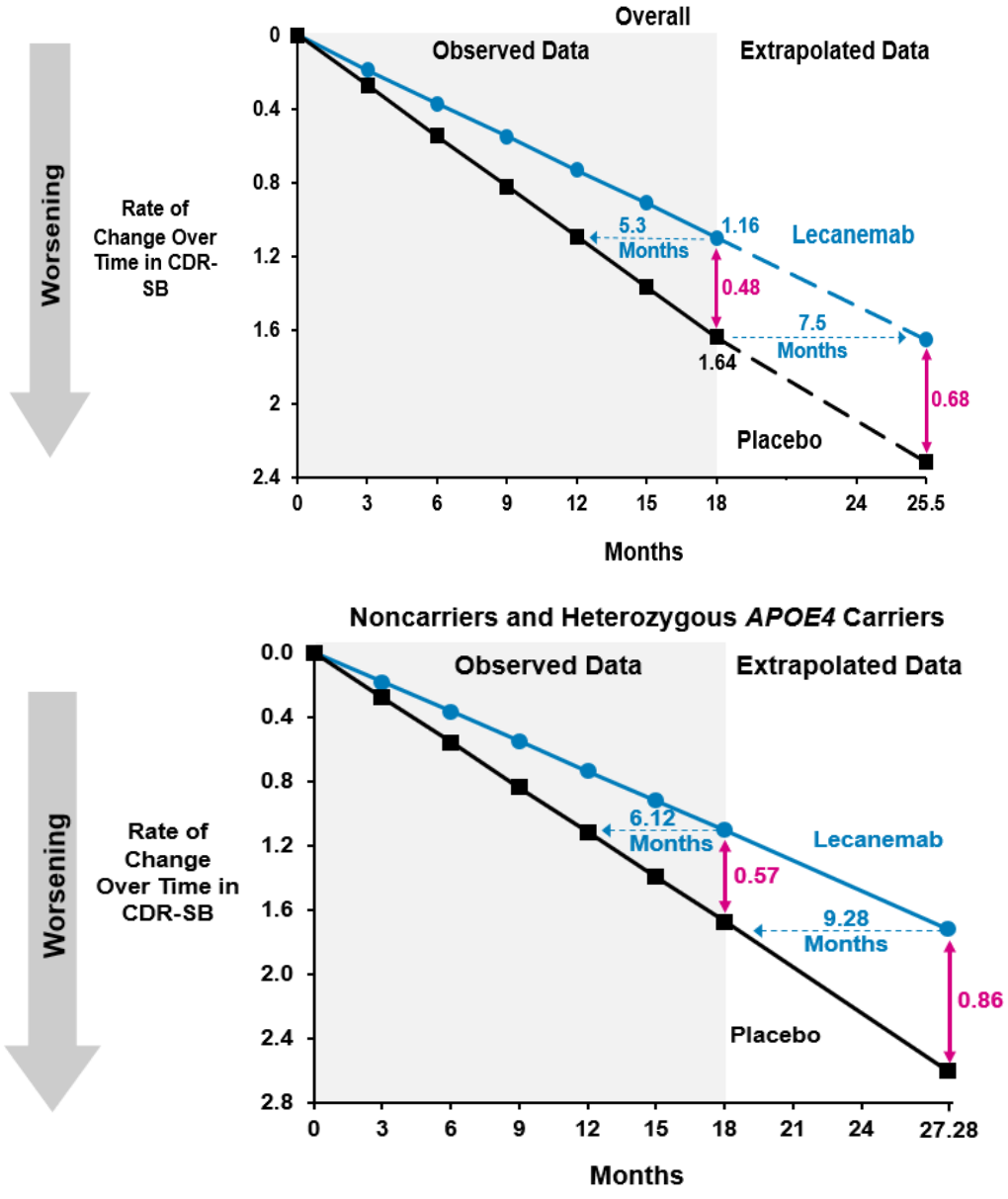


Figure 56. Analysis of rate of change over time of CDR-SB – study 301 core (mITT)

Change from baseline was analysed using LME model; LME model included time, and treatment by time as covariate with random intercept and slope.
APOE4 = apolipoprotein E4 variant, CDR-SB = Clinical Dementia Rating – Sum of Boxes, LME = linear mixed effects, mITT = modified intent to treat.
Source: Study 301 Core CSR Figure 4 and Appendix Table 14.2.3.2.1nh.

ADAS-Cog14

In the Overall Population, there is increasing separation over time between PBO and LEC10-BW. For ADAS-Cog14 there was 32.7% slowing of progression on LEC10-BW annually ([95% CI: 16.7% to 48.7%], *P*=0.00006) versus PBO (Figure 57). This separation indicates that cognition as assessed by ADAS-Cog14 is preserved by approximately 5.9 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 8.8 months to reach the clinical decline seen on PBO at 18 months (mean change in ADAS-Cog14 of 5.58).

In the Noncarrier and Heterozygous *APOE4* Carrier Population, there is increasing separation over time between PBO and LEC10-BW. For ADAS-Cog14 there was 35.4% slowing of progression on LEC10-BW annually ([95% CI: 18.2% to 52.5%], *P*=0.00005) versus PBO (Figure 57). This separation indicates that cognition as assessed by ADAS-Cog14 is preserved by approximately 6.4 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 9.9 months to reach the clinical decline seen on PBO at 18 months (mean change in ADAS-Cog14 of 5.85).

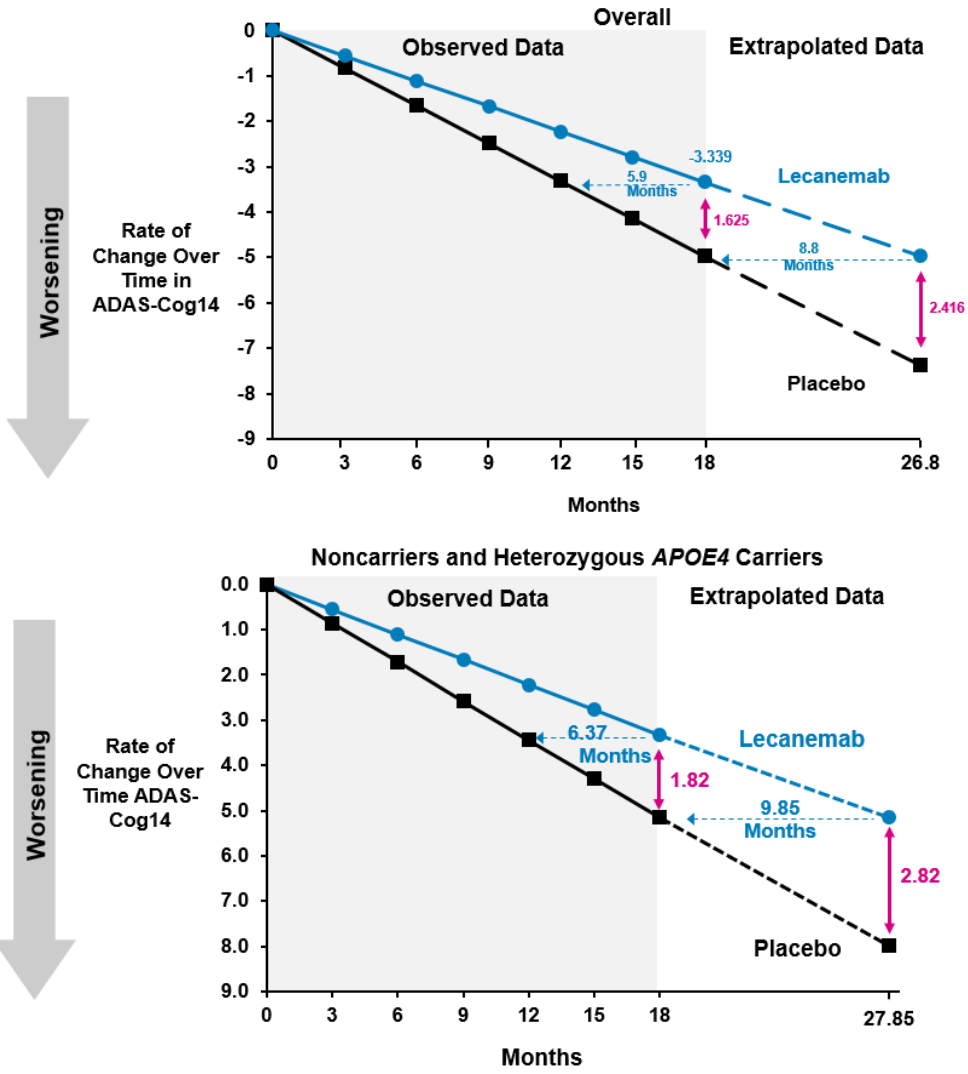


Figure 57. Analysis of rate of change over time of ADAS-Cog14 – study 301 core (mITT)

Change from baseline was analysed using LME model; LME model included time, and treatment by time as covariate with random intercept and slope.
APOE4 = apolipoprotein E4 variant, ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 item version, LME = linear mixed effects, mITT = modified intent to treat.
Source: Appendix 1 Table 14.2.3.10.1.

ADCS-MCI-ADL

In the Overall Population, there is increasing separation over time between PBO and LEC10-BW. For ADCS-MCI-ADL, there was 41.5% slowing of progression on LEC10-BW annually ([95% CI: 25.0% to 58.0%], *P*<0.00001) versus PBO (Figure 58). This separation indicates that function as assessed by ADCS-MCI-ADL is preserved by approximately 7.5 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 12.8 months to reach the clinical decline seen on PBO at 18 months (mean change in ADCS-MCI-ADL of -5.5).

In the Noncarrier and Heterozygous *APOE4* Carrier Population, there is increasing separation over time between PBO and LEC10-BW. For ADCS-MCI-ADL, there was 44.2% slowing of progression on LEC10-BW annually ([95% CI: 26.6% to 61.9%], *P*<0.00001) versus PBO (Figure 58). This separation indicates that function as assessed by ADCS-MCI-ADL is preserved by approximately 8 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an

additional 14.3 months to reach the clinical decline seen on PBO at 18 months (mean change in ADCS-MCI-ADL of -5.70).

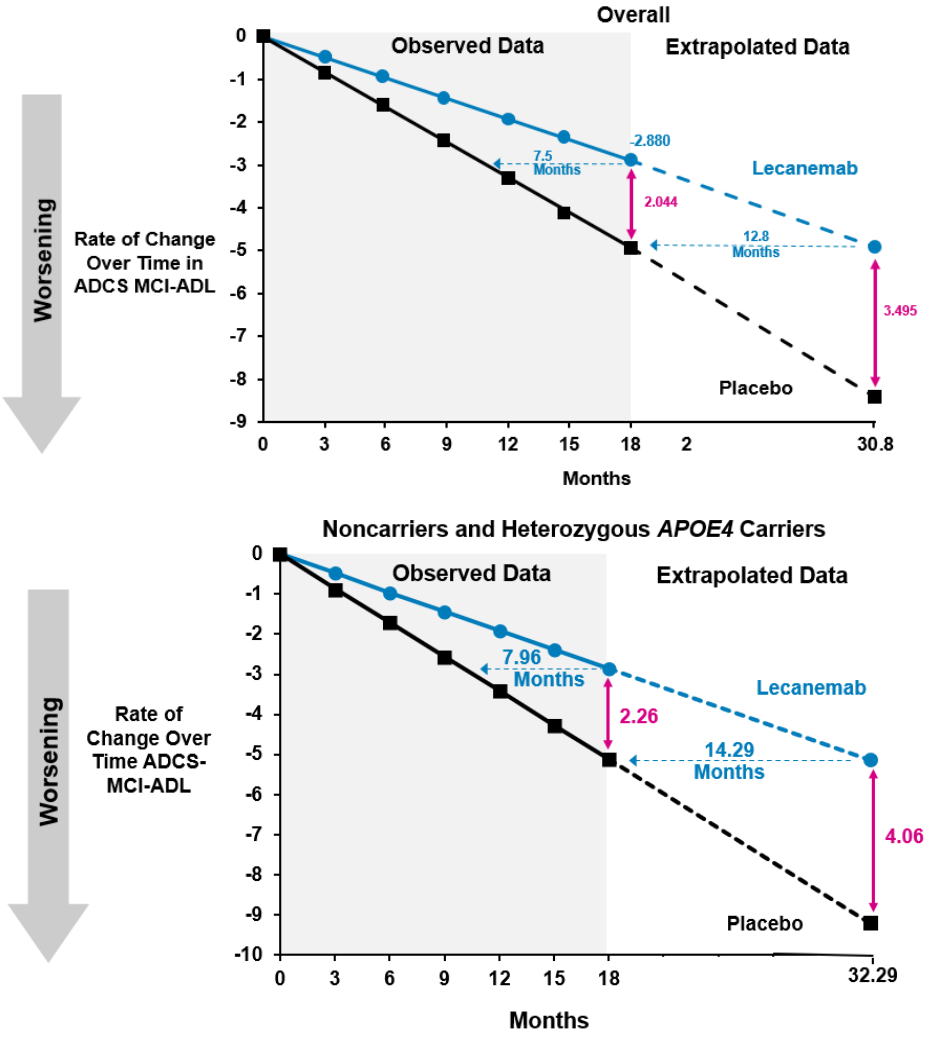


Figure 58. Analysis of rate of change over time of ADCS-MCI-ADL – study 301 core (mITT)

Change from baseline was analysed using LME model; LME model included time, and treatment by time as covariate with random intercept and slope.
APOE4 = apolipoprotein E4 variant, ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, LME = linear mixed effects, mITT = modified intent to treat.
Source: Appendix 1 Table 14.2.3.12.1.

(2) Time Saved: Long-Term Progression

The analyses and content contained in this section are new for the re-examination procedure.

At the early AD stage where progression rates in the absence of treatment are relatively slow (Figure 27), it is important to evaluate the relevance of an expanding treatment effect over time.

For the re-examination procedure, the applicant has performed an analysis on time to worsening to the next disease stage for CDR-SB using actual 36-month data for LEC10-BW and the ADNI natural history cohort and also incorporating 18-month PBO data from Study 301 Core to project time saved over 5 years after start of treatment (i.e., preserved cognition and function relative to PBO).

More information on the ADNI natural history cohort, including the a priori patient selection used to design Study 301 are provided in Section 0.

For this analysis CDR-SB was used rather than global CDR for disease staging. Weibull distribution was used to model the time to worsening to next disease stage adjusting for important covariates like baseline disease stage and *APOE4* carrier status. Weibull distribution follows proportional hazard assumption same as the time to worsening analysis using Cox regression approach.

As was shown by the analyses on time to worsening of global CDR score (Figure 47), neither treatment arm reached the median number of events by 18 months. The analyses performed by the applicant and shown in Figure 59 shows the time to worsening to next stage of disease with adjusted event rate through 60 months by treatment group, based on this model.

Based on this model, it is projected that ADNI natural history cohort/PBO arms reach the median number of events around 29 months whereas the LEC10-BW arm reaches median number of events at 41 months, 12 months later. This finding is again consistent with other analyses showing time saved on disease progression with LEC10-BW treatment.

Additionally, it is projected that 66% of ADNI natural history cohort/PBO subjects would convert to next stage of disease by 42 months, whereas it will take 60 months for 66% of LEC10-BW to convert. Thus, with LEC10-BW treatment there is 18 months saved on disease progression over a period of 5 years (i.e., the extent to which PBO subjects deteriorate would not be reached for LEC10-BW treated subjects for another 18 months).

This modelling approach provides additional insight into time saved on LEC10-BW treatment. The Applicant acknowledges that the results described are based on projections beyond the timeframe of patient follow-up, but the modelled survival distributions are a good fit to the observed data and the HR are proportional over time.

This analysis illustrates how the treatment effect observed with LEC10-BW at 18 months translates to a 5-year period of treatment and follow-up, demonstrating increasing benefit of treatment over time and a clinically relevant delay in disease progression with preservation of cognition and function relative to PBO.

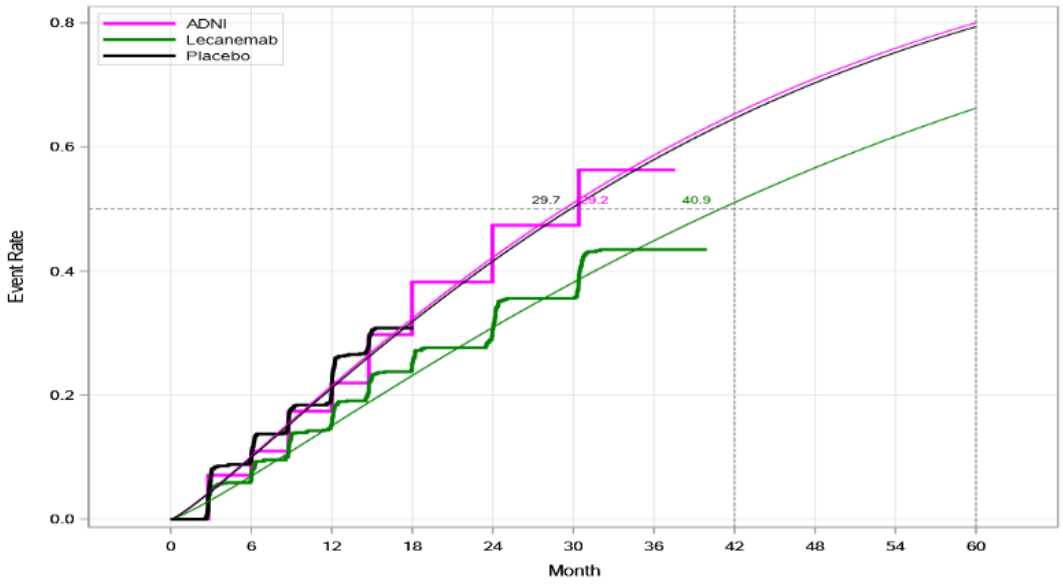


Figure 59. Event rate of time to worsening to next stage under Weibull distribution

Source: Data on file.

Table 95. Proportion of patients converting to the next stage of disease

Month	Lecanemab 10 mg/kg Biweekly	Placebo	ADNI
42	51.1%	65.4%	64.7%
60	66.3%	80.1%	79.4%

Source: Data on file.

(3) Limitations of Performing Restricted Mean Survival Time (RMST) Analysis for Early AD Clinical Studies

The analyses and content contained in this section are new for the re-examination procedure.

Previously presented time saved analyses (Section 0) are based on pre-specified slope analyses. Patients with early AD (MCI due to AD and mild AD dementia) are in the earliest stages of disease where disease progression is slow. The data for early AD subjects therefore meet proportional hazards assumption, hence the time saved analyses and associated metrics from a Cox PH model, HR are meaningful metrics to interpret slowing of disease progression (Section 0) by examining the proportion of subjects that progress to next stage of disease. Given the slow rate of disease decline in early AD, there were few subjects in either treatment arm that converted to the next stage of the disease (approximately 30% of PBO and 20% of LEC10-BW subjects converted from MCI to mild AD or mild AD to dementia), thus the median is not reached on either arm. In addition, since the earliest stages of AD are slow-moving, with the treatment effect expanding over time, it is important to assess the meaningful impact of treatment at a specific timepoint, for example after 18 months of treatment, rather than taking average across a treatment period.

RMST reflects the area under the survival curve (AUC) up to a specific time point (in this case, 18 months as the end of the randomised treatment period). It does not require the assumption of proportional hazards (indeed it is particularly useful if the proportional hazards assumption is in doubt) and does not therefore leverage the benefits inherent to that assumption. A particular limitation is that patients who do not experience the event of interest before the time horizon contribute to the AUC in each treatment group and hence reduce the estimated effect size. This is a limitation of the RMST approach: an effective treatment will also benefit patients who have not yet experienced an event, but that benefit is not captured by RMST, indeed the estimate of benefit to patients on average will be shrunk simply because those outcome times have not been observed. Hence this is not an appropriate method to evaluate the treatment effect over 18 months in early AD patients.

As described above, the time savings estimation methods directly compare the progression rates between groups, projecting how much earlier the PBO group reaches the same decline as the treatment group. This provides a quantification for how the effect of treatment on slowing progression of disease translates into the longer time for treated patients to stay at earlier stages of AD.

5.1.1.4.7. Changes in Health-Related Quality of Life Measures at 18 Months Further Characterise the Clinical Meaningfulness of Slowing of Cognitive and Function Decline in Alzheimer's Disease

Progression of AD is associated with worsening health-related quality of life. Maintaining health-related quality of life has been identified as a clinically meaningful benefit by both the patient and care partner, with health-related quality of life assessments providing unique perspectives from the patient and care partner with respect to their own perceptions of how the disease affects them (Lawton, 1994, Barbe, et al., 2018). The progression of disease is distressing for patients, their care partners, and their families. The increased dependency and emotional changes contribute significantly to care partner

burden, putting them at increased risk for physical morbidity and mental disorders (Sörensen and Conwell, 2011). Optimal management of AD should include the therapeutic goals of maintaining the patient's well-being and health-related quality of life.

Complementing the robust primary and secondary outcomes, the health-related quality of life assessments in Study 301 provide context and insights into both the disease impact, and the extent to which treatment can mitigate the loss decline of health-related quality of life even within an 18-month period. The primary and key secondary outcomes, along with these instruments, provide a comprehensive perspective on clinical meaningfulness.

In Study 301, LEC10-BW treatment was associated with a relative preservation of subject reported health-related quality of life and reduced progression of care partner burden relative to PBO. Consistent benefits were seen across different scales and within scales. At 18 months, the adjusted mean change from baseline in European Quality of Life-5 Dimensions 5 Level version (EQ-5D-5L) and Quality of Life in Alzheimer's disease (QOL-AD) rated by the patient showed 49% and 56% less decline, respectively. Study partner burden as measured by adjusted mean change from baseline at 18 months using the Zarit Burden Interview resulted in 38% reduction in care partner burden. For each health-related quality of life subject assessment, results favour of LEC10-BW beginning at 6 months Figure 60).

As shown above, the results on clinical scales at 18 months translate to tangible benefits for patients and their care partners as measured by health-related quality of life outcomes (Cohen, et al., 2023). Unlike for PBO subjects, those treated with LEC10-BW had less decline in mood, self-care, finances and life as a whole. For care partners, for whom AD has an enormous detrimental impact, fewer felt as if their quality of life had suffered.

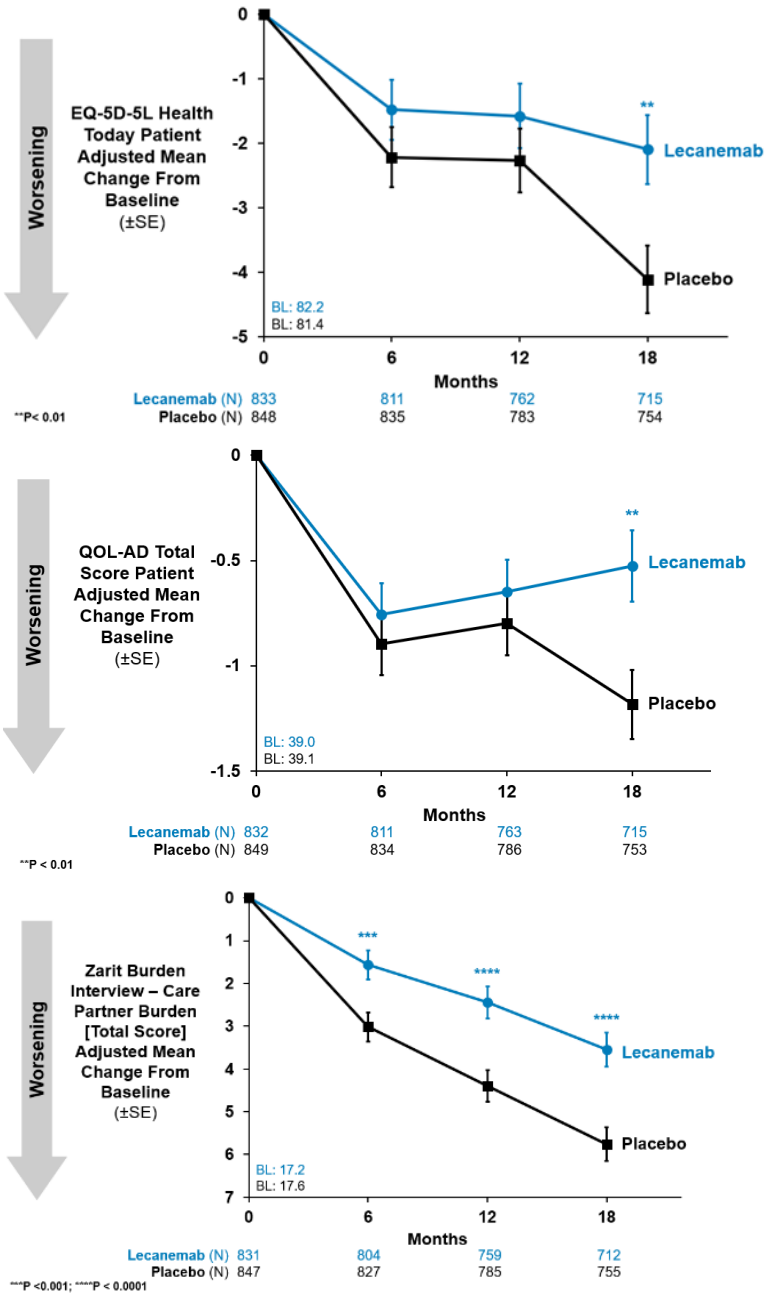


Figure 60. Health-related quality of life measures: EQ-5D-5L health today patient, QOL-AD total score patient and Zarit burden interview – study 301 core period (mITT)

EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level version, mITT = modified intent to treat, QOL-AD = Quality of Life in Alzheimer's Disease.
Source: Study 301 Core CSR Table 14.2.3.4.2, Table 14.2.3.5.2, and Table 14.2.3.6.2.

5.1.1.4.8. Additional Subgroup Analyses at 18 Months

(1) No/Low Tau PET Subgroup at 18 Months

The information contained herein was presented at AAIC 2024 (van Dyck, 2024) and is newly-provided as part of the re-examination procedure.

The revised diagnostic and staging criteria for AD recognises different biological stages based on the amount and distribution of tau tangles on tau PET:

- Early-stage: medial temporal tau
- Intermediate stage: moderate neocortical tau
- Advanced stage: high neocortical tau

The tau PET substudy of Study 301 included 342 patients with baseline tau PET scans, whose baseline characteristics were representative of the overall study population. The Applicant performed analyses stratified tau PET by no/low tau (consistent with early-stage), intermediate tau (consistent with intermediate-stage), and high tau (consistent with advanced stage) based on standardised uptake value ratio (SUVr). No/low tau (tau PET SUVr <1.06) tended to have no signal or restricted signal to transentorhinal cortex or hippocampus. Intermediate tau (SUVr 1.06-2.91) tended to have a signal in temporal and parietal neocortex. High tau (SUVr >2.91) tended to have a signal in temporal, parietal, and frontal cortex. Given there were no tau PET exclusion criteria in Study 301, approximately 41% of subjects in the Study 301 tau PET substudy had no/low tau PET levels (SUVr). The no/low tau population would likely be excluded from studies with tau PET exclusion criteria because this subgroup progresses more slowly, and it was presumed that it would be more difficult to detect a treatment effect over 18 months. Approximately 56% of subjects in the tau PET substudy had intermediate tau, and 3% had high tau.

CDR-SB at 18 Months in No/Low Tau PET Subjects

The following are post hoc analyses and no adjustment for multiplicity.

Figure 61 presents data from the no/low tau population in Study 301 Core (PBO N=67, LEC10-BW N=63). Data from this subgroup indicate that early initiation of therapy not only slows progression but can stabilise or even improve clinical outcomes:

- More subjects demonstrated no decline with LEC10-BW treatment than PBO on CDR-SB at 18 months (PBO: 32/58, 55%; LEC10-BW: 38/50, 76%) at 18 months.
- More subjects demonstrated an improvement with LEC10-BW treatment than PBO on CDR-SB (PBO: 16/58, 28%, LEC10-BW: 30/50, 60%) at 18 months.

For no/low tau subjects the results seen at 18 months were sustained though 36 months (Section 0).

Similar results were seen for ADAS-Cog14 and ADCS-MCI-ADL as presented in Appendix 5 Section 14.

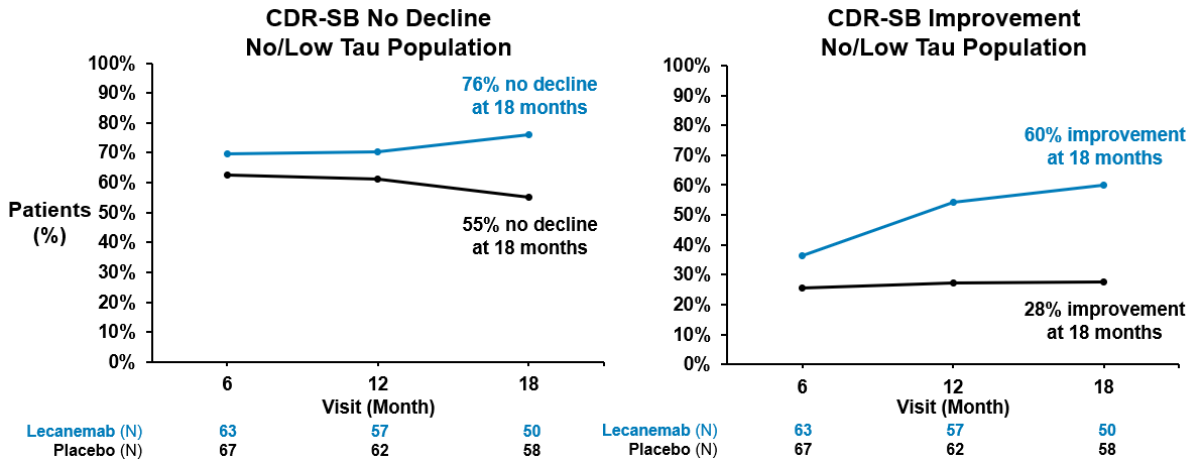


Figure 61. CDR-SB at 18 months in no/low Tau PET subjects – study 301 core (Tau PET substudy)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, PET = positron emission tomography.
Source: Appendix 1 Table 14.2.1.1.3is.

(2) Low Amyloid Subgroup at 18 Months

CDR-SB at 18 Months in Low Amyloid Subjects

The information contained herein was presented at AAIC 2024 (van Dyck, 2024) and is newly-provided as part of the re-examination procedure.

Brain amyloid is a defining pathological feature of AD that precedes and predisposes to tauopathy, neurodegeneration, and cognitive decline. These concepts have been incorporated in the NIA-AA (Jack, et al., 2024) research framework whereby an AT(N) biomarker profile with 'A' denoting amyloid, 'T' aggregated tau, and 'N' neurodegeneration, can be used to characterise the AD continuum, with the presence of amyloid considered a necessary requirement.

Evaluating the levels of amyloid in relation to the levels of tau in the tau PET substudy of Study 301, a threshold of <60 centiloids of amyloid defines a subgroup enriched for no/low tau and reflects an early pathological stage of disease.

In Study 301, N=376 subjects had low amyloid at baseline. The baseline characteristics for these subjects are provided in Appendix 1 Table 14.1.4.1.1ltla and Appendix 1 Table 14.1.4.1.4ltla.

CDR-SB at 18 Months in Low Amyloid PET Subjects

The following are post hoc analyses and no adjustment for multiplicity.

Figure 62 presents data from the low amyloid population (<60 CL population in Study 301 Core (PBO N=176, LEC10-BW N=178). Data from this subgroup indicate that early initiation of therapy not only slows progression but can stabilise or improve clinical outcomes:

- More subjects demonstrated no decline with LEC10-BW treatment than PBO on CDR-SB (PBO: 75/161, 46.6%; LEC10-BW: 85/146, 58.2%) at 18 months.
- More subjects demonstrated an improvement with LEC10-BW treatment than PBO on CDR-SB (PBO: 41/161, 25.5%, LEC10-BW: 54/146, 37.0%) at 18 months.

The results seen at 18 months were sustained though 36 months (Section 0).

Similar results were seen for ADAS-Cog14 and ADCS-MCI-ADL as presented in Appendix 5 Section 15.

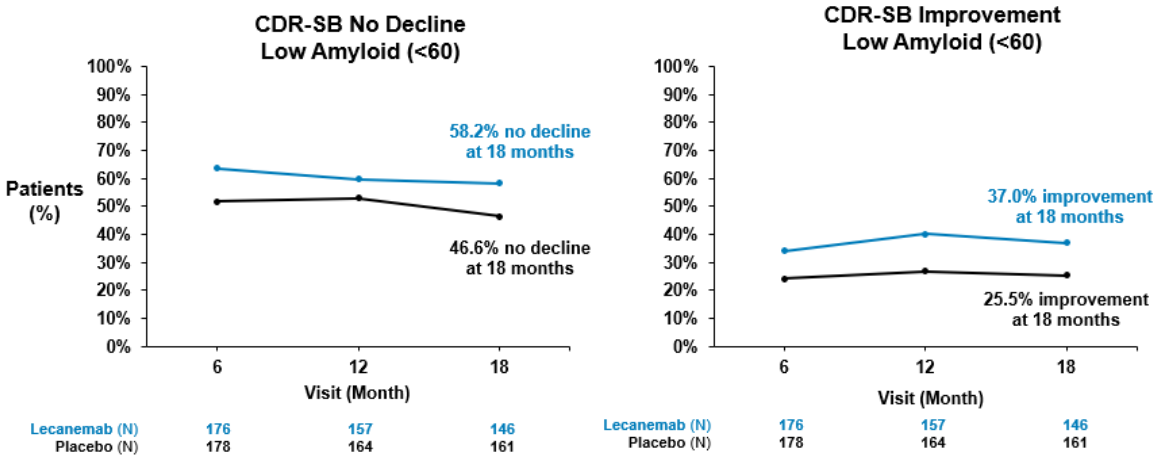


Figure 62. CDR-SB at 18 months in low amyloid PET subjects – study 301 core (amyloid PET substudy)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, PET = positron emission tomography.
Source: Appendix 1 Table 14.2.1.1.3is.

5.1.1.4.9. Lecanemab Treatment Effect is Sustained Through 36 Months

The analyses for Noncarrier and Heterozygous *APOE4* Carrier Population, individual genotypes and the detailed description of ADNI in this section are new for the re-examination procedure.

Study 301 Core and OLE Phase data show that LEC10-BW treatment results in accumulating benefit compared to natural disease progression through 36 months:

- The treatment effect of LEC10-BW versus PBO at the end of the 18-month Study 301 Core Study was maintained when both arms were treated with LEC10-BW from 18 to 36 months.
- The treatment difference seen at 18-months for both the Overall and Noncarrier and Heterozygous *APOE4* Carrier Populations (-0.45 and -0.58, respectively) continues to expand through 36 months when compared to a natural history cohort in the OLE Phase, with a treatment difference of -0.95 (Overall Population) and -0.86 (Noncarrier and Heterozygous *APOE4* Carrier Population) at 36 months.
- Delayed-start analyses for CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL demonstrate that the slowing of disease progression seen at 18 months with LEC10-BW versus PBO is maintained while both arms were treated with LEC10-BW from 18 to 36 months. Subjects with delayed initiation of treatment do not recover to the level of subjects with early initiation of treatment. The results of these delayed-start analyses are consistent with a disease modifying effect and highlight the detrimental effects of delaying treatment in early AD.
- The early start patients (those who were on LEC10-BW in the Core) continue to separate from a natural history cohort in the OLE Phase through 36 months. Even the late start patients (those who were on PBO during the Core) begin to separate from a natural history cohort after initiating LEC10-BW in the OLE Phase.

(1) Study 301 Results at 36 Months for CDR-SB

ADNI Cohort Selection and Baseline Characteristics

Since there is not a PBO group during the OLE phase between 18 and 36 months, an observational cohort (Alzheimer's Disease Neuroimaging Initiative [ADNI]) of early AD patients established prior to the start of Study 301 is used to assess the effect of long term LEC10-BW treatment relative to the natural history of decline on CDR-SB.

The ADNI study, with data from over 60 clinical sites in the USA and Canada, actively supports the investigation and development of treatments that slow the progression of AD. The ADNI study tracks the progression of the disease across normal aging, MCI, and AD and dementia using biological markers (biomarkers; for example, chemicals found in blood, or changes to the brain observed in imaging studies such as magnetic resonance imaging [MRI] and PET scans), together with clinical measures (cognitive and neuropsychological tests), to assess the brain's structure and function over the course of three disease states (cognitively normal/unimpaired, mild cognitive impairment, dementia). ADNI provides study data and biospecimens (samples) to qualified researchers worldwide. Throughout the development of lecanemab, the applicant has used data from the ADNI study to aid in decision-making for the programme (for example, for estimations of PBO decline to aid in power calculations [Scientific Advice Background Package 2013 and 2018]).

The Applicant used the ADNI cohort to design Study 301, selecting *a priori* a representative early AD observational cohort from ADNI and then using this longitudinal data to create simulations of progression over an 18-month period. The observational cohort criteria matched the planned key inclusion criteria and study population for Study 301:

(1) baseline diagnosis of "MCI" with global CDR = 0.5 and CDR memory ≥0.5 or baseline diagnosis of "AD" with global CDR = 0.5 or 1.0 and CDR memory ≥0.5

(2) proportion of MCI (60%) and mild AD (40%)

(3) baseline Mini-Mental State Examination (MMSE) ≥22

(4) at least 1 of 2 criteria for amyloid positivity

(4a) baseline amyloid PET SUVr florbetapir ≥1.11 or amyloid PET SUVr Pittsburgh compound B (PIB) ≥1.47 or

(4b) baseline cerebrospinal fluid (CSF) total tau/amyloid beta (Aβ)>0.222

Of the ADNI cohort, the applicant used all 436 patients who met these criteria. ADNI data were downloaded in Feb 2020, with ADNI cohort generated soon after the data download, and used to apply the above eligibility criteria. Using this ADNI cohort, the rate of decline at 18 months and variability in the data was estimated for power calculations in Study 301. Study 301 Core completed recruitment in Mar 2021 with database lock in Sep 2022.

The same patient cohort has been followed by ADNI for several years and the study continues. As can be seen from Table 96, the baseline demographic and clinical characteristics are similar between Study 301 Core and the pre-specified ADNI cohort.

Table 96. Baseline demographic and clinical characteristics – study 301 core and ADNI

Category	**Study 301 Combined Total (Lecanemab 10 mg/kg Biweekly and Placebo)**	**ADNI**
N	1795	436
Age		
Mean (SD)	71.3 (7.83)	73.8 (7.38)
Median	72.0	74.4
APOE4 Carrier Status		
Positive n (%)	1231 (68.6)	305 (70.0%)
Negative n (%)	564 (31.4)	131 (30.0%)
Disease Stage[a], n (%)		
MCI due to AD	1107 (61.7)	267 (61.2%)
Mild AD	688 (38.3)	169 (38.8%)
Baseline CDR-SB		
Mean (SD)	3.20 (1.340)	2.66 (1.662)
Median	3.00	2.50

AD = Alzheimer's disease, ADNI = Alzheimer's Disease Neuroimaging Initiative, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, LEC10 BW = lecanemab 10 mg/kg biweekly, MCI = mild cognitive impairment, OLE = open-label extension, PBO = placebo, SD = standard deviation.
Age is calculated at date of informed consent in Core Study for Study 301 Core, and at enrolment for ADNI.
a: Disease stage in Study 301 was collected at baseline in Core Study.
Source: Study 301 Core CSR Tables 14.1.4.1.3, 14.1.4.1.6; ADNI 2020 data download.

Furthermore, Figure 63 shows that the decline in CDR-SB in the ADNI cohort exactly overlies the PBO in Study 301, as predicted for the 18-month Core. This provides confidence that the matching criteria was successful and that the ADNI cohort is representative of the population recruited into Study 301.

Results for CDR-SB

Figure 63 and Figure 64 presents the change from baseline for CDR-SB at 36 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Results were consistent

across both populations, with separation between the early start (subjects treated with LEC10-BW during the Core) and delayed start (subjects treated with PBO during the Core and subsequently treated with LEC10-BW in the OLE Phase) maintained between 18 and 36 months when all subjects received LEC10-BW. Parallel disease trajectory is observed for the early start and delayed start between 18 to 36 months.

- For the Overall Population (Appendix 1 Table 14.2.1.1.2is and Appendix 1 Table 14.2.1.1.4):
    - At 36 months, the adjusted mean treatment difference was -0.95 between LEC10-BW and the ADNI cohort with 7.6 months' time saved. This represents more than half a year that LEC10-BW subjects remain with preserved cognition and function relative to PBO, highlighting the importance of continuous therapy with LEC10-BW.
- For the Noncarrier and Heterozygous *APOE4* Carrier Population (Appendix 1 Table 14.2.1.1.2isnh and Appendix 1 Table 14.2.1.1.4nh):
    - The adjusted mean treatment difference was -0.86 between LEC10-BW and the ADNI cohort with 6.8 months' time saved.

Over time the difference between the LEC10-BW treated group, and the natural history (ADNI) cohort will continue to increase, given the known acceleration of AD (Figure 27).

Individual genotypes are presented in Appendix 5 Section 16.

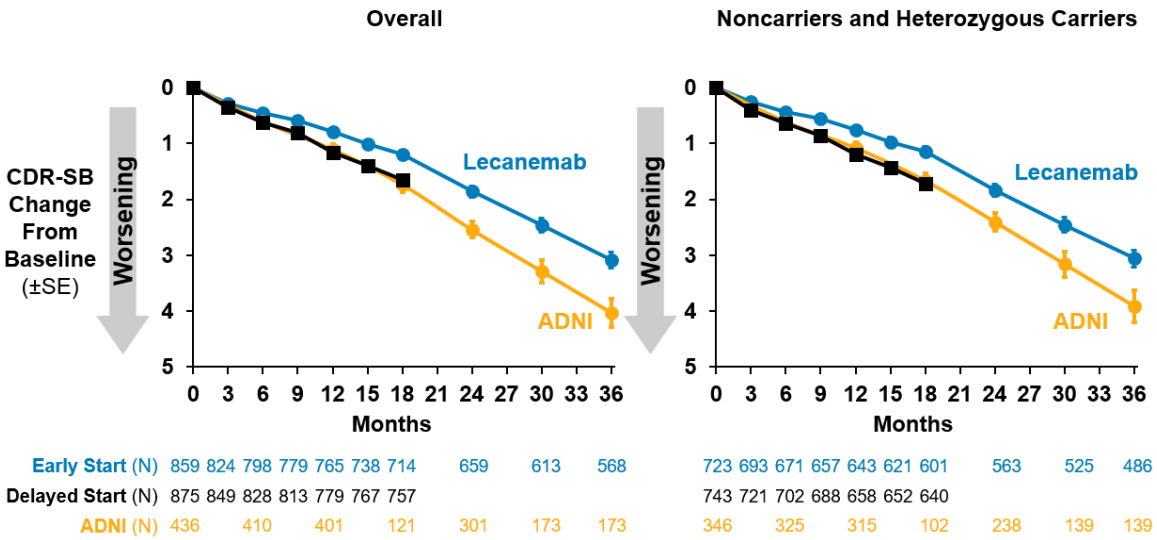


Figure 63. Adjusted mean change from baseline in CDR-SB in context of observational cohort through 36 months – study 301 core and OLE phase (mITT)

ADNI = Alzheimer's Disease Neuroimaging Initiative, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, mITT = modified intent to treat, OLE = open-label extension, SE = standard error.
Includes intravenous and subcutaneous-treated subjects.
Source: Appendix 1 Table 14.2.1.1.2is, Appendix 1 Table 14.2.1.1.2isnh, Appendix 1 Table 14.2.1.1.4, and Appendix 1 Table 14.2.1.1.4nh.

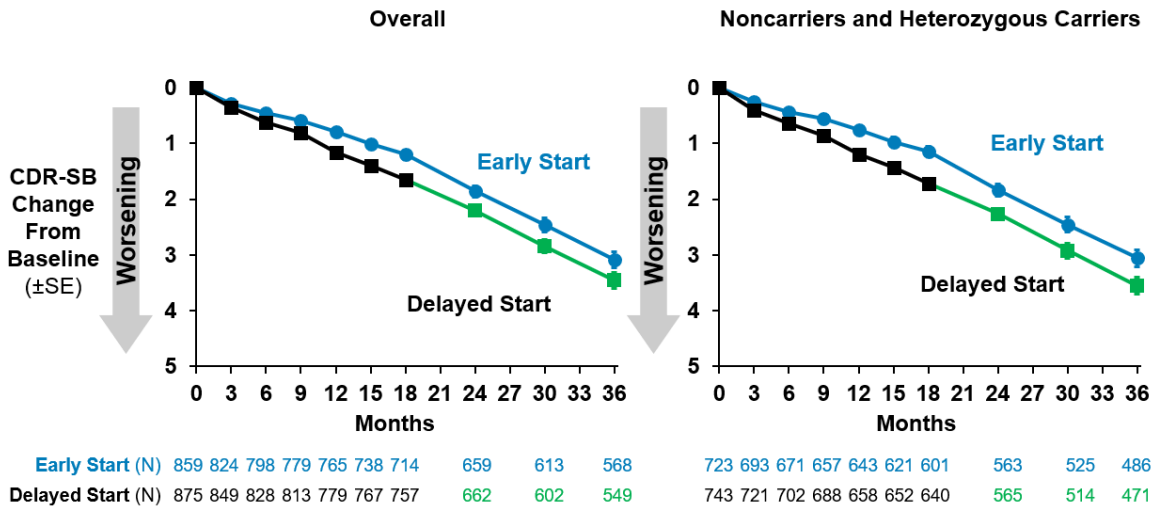


Figure 64. Adjusted mean change from baseline in CDR-SB through 36 months – study 301 core and OLE phase (mITT)

(2) Study 301 Results at 36 Months for ADAS-Cog14

An ADNI line is not provided for ADAS-Cog14 as this specific scale is not captured in the observational cohort.

Figure 65 presents the change from baseline for ADAS-Cog14 at 36 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Consistent with what was seen for CDR-SB, results were consistent across both populations, with separation between the early start and delayed start maintained between 18 and 36 months when all subjects received LEC10-BW, with a parallel disease trajectory observed for the early start and delayed start between 18 to 36 months.

- For the Overall Population the adjusted mean treatment difference was -1.10 between LEC10-BW early start and the delayed start (Appendix 1 Table 14.2.3.1.2is).
- For the Noncarrier and Heterozygous *APOE4* Carrier Population the adjusted mean treatment difference was -1.56 between LEC10-BW early start and the delayed start (Appendix 1 Table 14.2.3.1.2isnh).

Individual genotypes are presented in Appendix 5 Section 17.

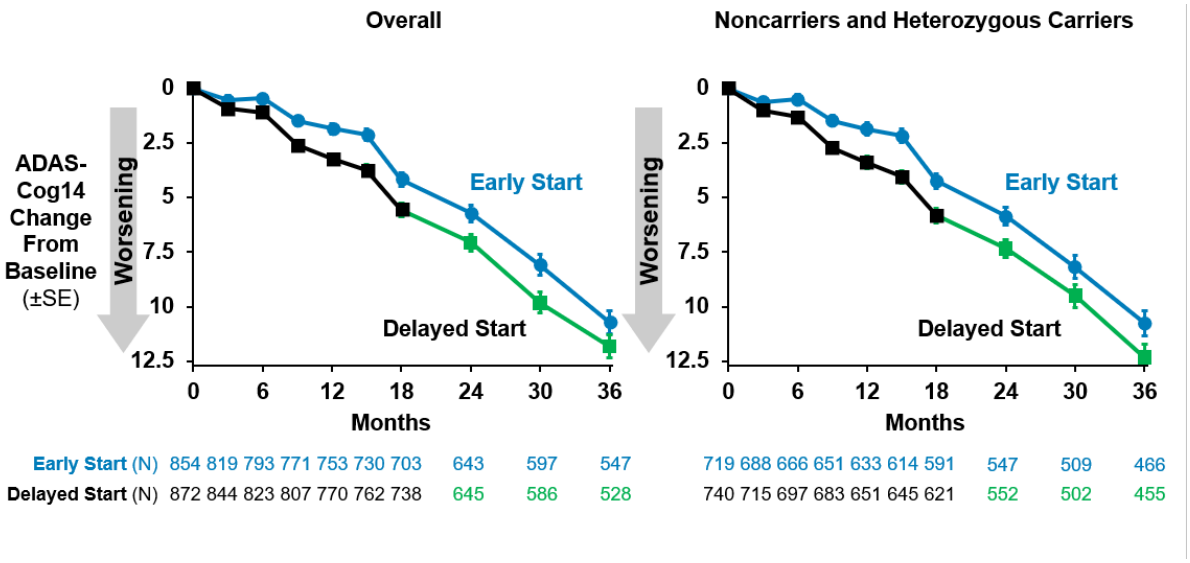


Figure 65. Adjusted mean change from baseline in ADAS-Cog14 through 36 months – study 301 core and OLE phase (mITT)

ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale 14-item version, *APOE4* = apolipoprotein E4, mITT = modified intent to treat, OLE = open-label extension, SE = standard error.
Includes intravenous and subcutaneous-treated subjects.
Source: Appendix 1 Table 14.2.3.1.2is and Appendix 1 Table 14.2.3.1.2isnh.

(3) Study 301 Results at 36 Months for ADCS-MCI-ADL

An ADNI line is not provided for ADCS-MCI-ADL as this specific scale is not captured in the observational cohort.

Figure 66 presents the change from baseline for ADCS-MCI-ADL at 36 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. Consistent with what was seen for the other scales, results were consistent across both populations, with separation between the early start and delayed start maintained between 18 and 36 months when all subjects received LEC10-BW, with a parallel disease trajectory observed for the early start and delayed start between 18 to 36 months.

- For the Overall Population the adjusted mean treatment difference was 1.80 between LEC10-BW early start and delayed start (Appendix 1 Table 14.2.3.3.2is).
- For the Noncarrier and Heterozygous *APOE4* Carrier Population the adjusted mean treatment difference was 1.80 between LEC10-BW early start and delayed start (Appendix 1 Table 14.2.3.3.2isnh).

Individual genotypes are presented in Appendix 5 Section 18.

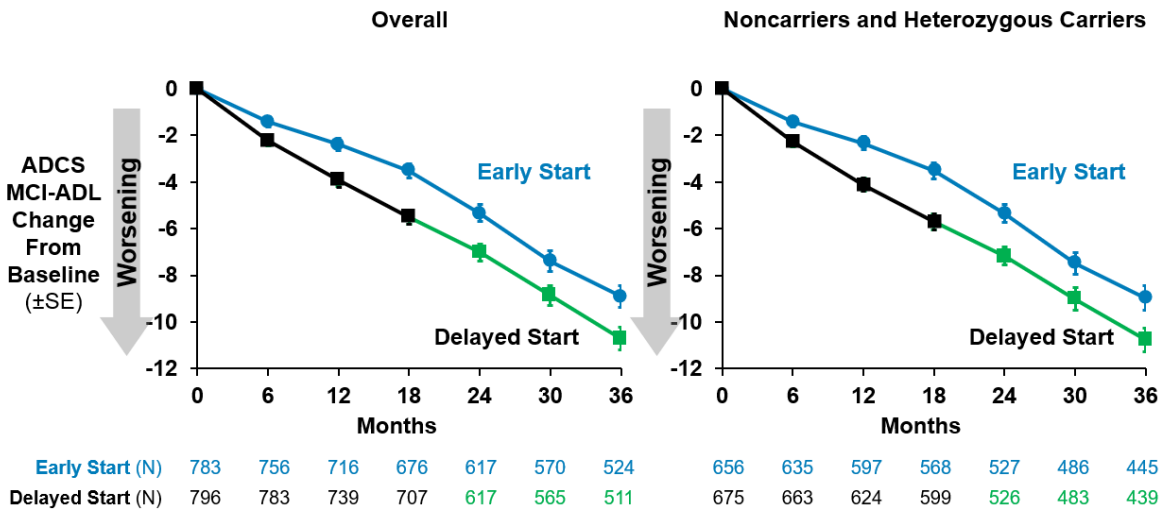


Figure 66. Adjusted mean change from baseline in ADCS-MCI-ADL – study 301 core and OLE phase (mITT)

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for use in Mild Cognitive Impairment, *APOE4* = apolipoprotein E4, mITT = modified intent to treat, OLE = open-label extension, SE = standard error.
Includes intravenous and subcutaneous-treated subjects.
Source: Appendix 1 Table 14.2.3.3.2is and Appendix 1 Table 14.2.3.3.2isnh.

(4) Lecanemab Continues to Delay Disease Progression Through 36 Months as Measured by Time to Worsening on CDR-SB

The analyses and content contained in this section are new for the re-examination procedure.

To provide clinical relevance of the group-level difference at 36 months, the applicant conducted an analysis on time to worsening to the next disease stage (based on CDR-SB) relative to the ADNI natural history cohort. Since controlled-based imputation was used for missing data in this analysis (especially for less frequent ADNI assessments), CDR-SB was used rather than global CDR for disease staging. Time to worsening was defined as CDR-SB score progressing from MCI (range 0.5 – 4) to dementia (range >4.0) or mild dementia (4.5 - 9.0) to moderate/severe dementia (>9.0) based on dementia staging on CDR-SB. Figure 67 shows:

- In the Overall Population, LEC10-BW reduced the risk of progression to the next stage of AD on CDR-SB score by 31% (i.e., from MCI to dementia or from mild AD to moderate or severe dementia). The HR of disease progression on CDR-SB is 0.692 (95% CI [0.580, 0.825]), representing 31% lower risk on LEC10-BW as compared to the ADNI natural history cohort.
- In the Noncarrier and Heterozygous *APOE4* Carrier Population LEC10-BW reduced the risk of progression to the next stage of AD on CDR-SB score by 28%. The HR of disease progression on CDR-SB is 0.718 (95% CI [0.589, 0.874]), representing 28% lower risk on LEC10-BW as compared to the ADNI natural history cohort.

This time to event analysis demonstrates that LEC10-BW maintains subjects at an earlier stage of disease where they are more independent. It provides the clinical relevance of the primary outcome (which is also supported by key secondary endpoints and subject-reported health-related quality of life outcomes).

Individual genotypes are presented in Appendix 5 Section 19.

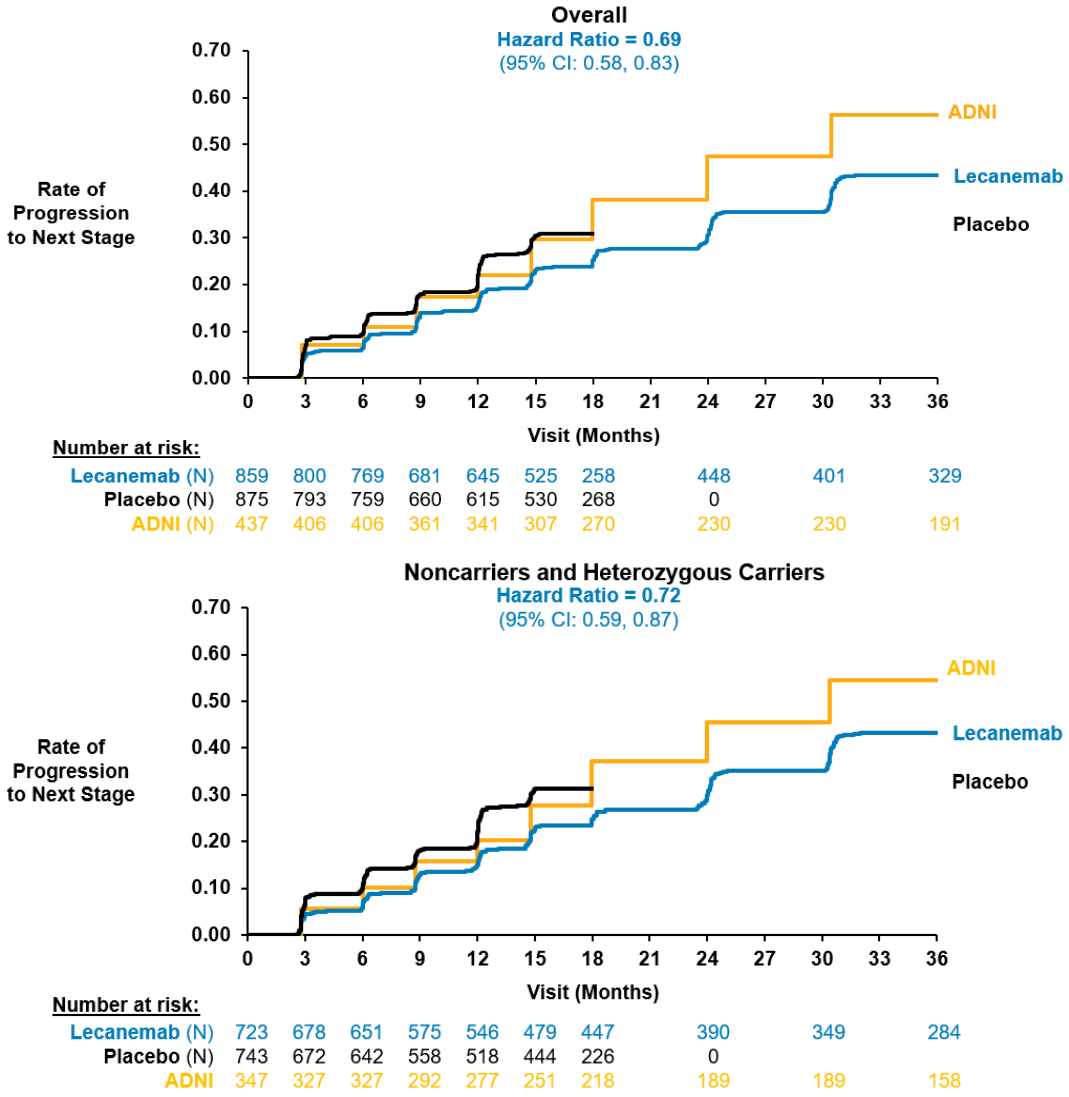


Figure 67. Kaplan–Meier curves for time to worsening of CDR-SB score through 36 months – study 301 core and OLE phase (mITT) – overall population

Data presented include Cox regression model includes *APOE4* carrier status and clinical subgroup.
ADNI = Alzheimer's Disease Neuroimaging Initiative, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating –Sum of Boxes, mITT = modified intent to treat, OLE = open-label extension.
Source: Appendix 1 Figure 14.2.3.7.1nh.

(5) Additional Subgroup Analyses at 36 Months

The information contained herein was presented at AAIC 2024 (van Dyck, 2024) and is newly-provided as part of the re-examination procedure.

No/Low Tau PET Subgroup at 36 Months

CDR-SB at 36 Months in No/Low Tau PET Subjects

The results seen at 18 months for the no/low tau subgroup (Section 0) were sustained through 36 months (Figure 68):

- At 36 months, 24/41, 59% of subjects demonstrated no decline on CDR-SB with LEC10-BW.
- At 36 months 21/41, 51% of subjects continued to show improvement on CDR-SB with LEC10-BW.

Similar results were seen for ADAS-Cog14 and ADCS-MCI-ADL as presented in Appendix 5 Section 20.

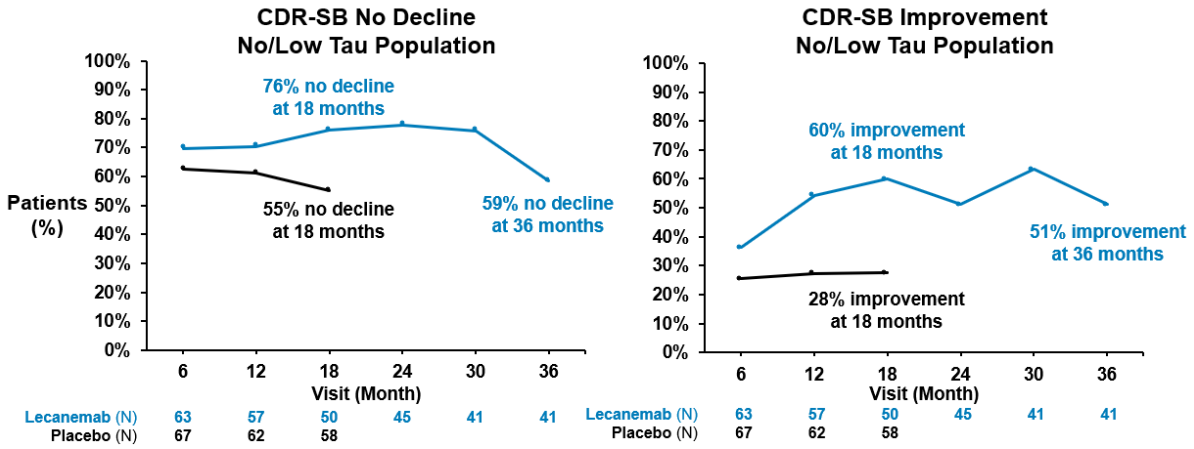


Figure 68. CDR-SB at 36 months in no/low Tau PET subjects – study 301 core and OLE phase (Tau PET substudy)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, PET = positron emission tomography.
Source: Appendix 1 Table 14.2.1.1.3is.

Low Amyloid Subgroup at 36 Months

CDR-SB at 36 Months in Low Amyloid Subjects

The results seen at 18 months for the low amyloid PET subgroup (Section 0) were sustained through 36 months (Figure 69):

- At 36 months, 53/115, 46.1% of subjects demonstrated no decline with LEC10-BW.
- At 36 months 38/115, 33.0% of subjects continued to show improvement on CDR-SB.

Similar results were seen for ADAS-Cog14 and ADCS-MCI-ADL as presented in Appendix 5 Section 21.

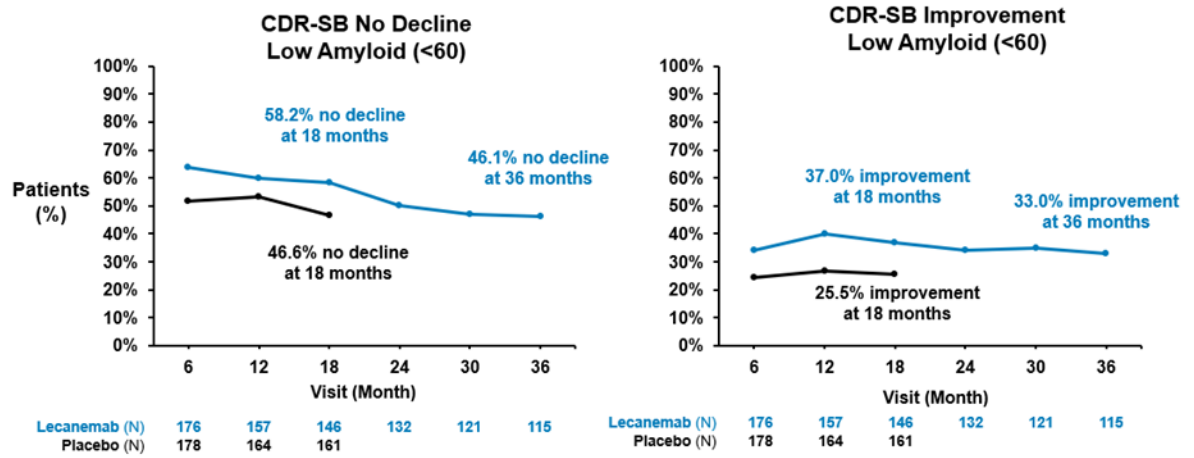


Figure 69. CDR-SB at 36 months in low amyloid PET subjects – study 301 core and OLE phase (amyloid PET substudy)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, PET = positron emission tomography.
Source: Appendix 1 Table 14.2.1.1.3is.

5.1.1.4.10. Efficacy Conclusion

LEC10-BW demonstrated slowing in disease progression of 26%– 37% across the primary and key secondary endpoints at the group-level in the Overall Population, and 28%– 39% in the Noncarrier and Heterozygous *APOE4* Carrier Population. Results remained consistent across Overall Population and Noncarrier and Heterozygous *APOE4* Population, demonstrating similar efficacy benefit across genotypes.

To assist in the interpretation of the treatment effects, the applicant performed time to progression to clinically meaningful milestones, responder/progressor and time saved analyses for all key clinical scales.

Results from all analyses demonstrate that regardless of the clinically meaningful threshold or milestone, and across multiple endpoints, LEC10-BW demonstrates consistent clinically relevant slowing of disease progression. Slowing of disease progression is inherently meaningful for patients as it means that their cognitive and functional abilities are maintained for longer, allowing patients to live a more enriched, independent life for longer duration. With LEC10-BW treatment there was a reduced relative risk of clinical decline at every threshold, and the higher the threshold (i.e., more decline), the greater the relative risk reduction. The slowing of progression, with preserved cognition and function, can also be considered as "time saved". Over an 18-month treatment period, in the Noncarrier and Heterozygous *APOE4* Carrier Population, LEC10-BW subjects had 6.1 – 8.0 months retained cognition and function relative to PBO.

With a treatment that has an effect on underlying disease pathophysiology, the treatment effects are expected to increase over time. This increase over time is evident from the 36-month OLE Phase data which shows that the effect on clinical scales seen at 18 months are sustained and when compared to a natural history cohort (ADNI, selected a priori to initiation of Study 301 to aid in the design of the study), the treatment effect seen at 18 months increases over time. In time to conversion to the next stage of disease over 5 years, time saved is projected to be 18 months, keeping patients at earlier stage of disease for additional 1.5 years. When put in context with progression free survival used for in oncology studies, this is a meaningful gain for early AD patients. Additional time saved allows patients continued independence and the self-autonomy to manage their usual activities (such as working [if not retired], driving, personal care [toileting, bathing], continuing intellectual interests, volunteer and social group participation).

Consistent with the responder/progressor analyses, health-related quality of life outcomes reinforce that the changes seen on clinical scales after 18 months translate to tangible, meaningful benefits for patients and their care partners. Long-term data show that these benefits continue to increase over time. Those treated with LEC10-BW had less decline in mood, self-care, finances and life as a whole relative to PBO. For care partners, for whom AD has an enormous detrimental impact, fewer felt as if their quality of life had suffered.

In conclusion, the convergence of evidence supports that the treatment effects seen at 18months result in meaningful benefits for patients whereby they are able to maintain their cognitive and functional abilities for longer, and that that the meaningful benefits seen at 18 months continue to increase over time.

5.1.1.5. Homozygous APOE4 Carriers

Individuals with 2 *APOE4* alleles are at highest risk for developing AD (14-fold risk over noncarriers) (Hunsberger, et al., 2019; Fortea, et al., 2024), with an earlier age of onset (approximately 10 years earlier than noncarriers), higher levels of amyloid accumulation, greater burden of CAA, and greater risk of spontaneous ARIA even in the absence of anti-amyloid therapies.

In the grounds for refusal the CHMP specifically cited concerns regarding ARIA in homozygous *APOE4* carriers. The CHMP have also noted the lower estimated effect sizes in this subgroup for some efficacy variables.

The applicant acknowledges the different risk for ARIA in homozygous *APOE4* carriers and has proposed a narrower indication accordingly.

However, the applicant retains the opinion that the effects of LEC10-BW are the same regardless of *APOE4* carrier status and genotype: results for homozygous *APOE4* carriers appear to be a play of chance (response to 2nd D180 question 3). This is supported by a similar effect of LEC10-BW on ADAS-Cog14, ADCS MCI-ADL, and all biomarkers (amyloid positron emission tomography [PET], plasma Aβ42/40 ratio, phosphorylated tau at residue 181 [plasma p-tau 181]), effects estimated in the 856-subject Phase 2 study (Study 201) and results from trials of other anti-amyloid therapies in this target population that show no effect modification.

Indeed, the rate of progression of PBO homozygous *APOE4* carriers is an outlier, reflecting a 'random low' in comparison to expectations from clinical understanding and other clinical trial data. This result impacts not only the estimate for the treatment effect in homozygous *APOE4* carriers, but the result of the primary analysis.

Since the applicant has proposed a narrower indication, this request for re-examination presents results for the Overall Population, as well as for the proposed population, Noncarrier and Heterozygous *APOE4* Carriers. The applicant recognises the considerations regarding the interpretation of subgroups in line with European Medicines Agency (EMA) guidance (EMA, 2019). Given the clear explanation of the lower estimated effects in homozygous *APOE4* carriers on CDR-SB, the applicant considers the estimates from proposed patient population subgroup, Noncarrier and Heterozygous *APOE4* Carrier Population, to be interpretable ("credible" per CHMP's guideline).

In the opinion of the applicant, treatment effects are of clinically relevant magnitude whether the interpretation of efficacy is based on the Overall Population, or the Noncarrier and Heterozygous *APOE4* Carrier Population.

For this patient population, who have an earlier age of onset of AD, it is important to balance the rare serious events of ARIA against the majority of ARIA events, which resolve without symptoms or clinical sequelae.

5.1.2. Clarifications and proposals submitted during the re-examination procedure

5.1.2.1. Summary of post-marketing safety data

The Applicant presented as clarification a summary of the post-marketing data previously submitted. In the below sections, the information submitted is reported.

5.1.2.1.1. Cumulative and Interval Patient Exposure from Marketing Experience

There were over 140,000 vials dispensed as either 200 mg/2ml or 500 mg/5ml doses in the US and China during the report period. Based on the number of vials dispensed, the recommended dose of 10 mg/kg and an assumption of an average patient weight of 70 kg, it is calculated that there were over 59,000 doses dispensed during the reporting period. Cumulatively there have been approximately 180,000 vials, which is estimated to be over 75,000 doses, dispensed from IBD until DLP.

There were approximately 35,000 vials dispensed in Japan during the report period and cumulatively to treat approximately 2440 patients.

During the current reporting period, worldwide patient exposure to lecanemab is estimated to be over 72,000 doses. The cumulative worldwide patient exposure to lecanemab from the International Birth Date (IBD) is estimated to be over 89,000 doses.

The post-marketing exposure data are not available as broken down by sex, age, indication or the actual number of patients exposed.

5.1.2.1.2. Evaluation of Risks and New Information

For the events described below a search of the global lecanemab adverse event report database was performed for all reports from post marketing sources as well as serious reactions reports from non-interventional trials. In addition, relevant data from interventional clinical trials is included when informative. Cumulative reviews include data from US approval/IBD, 06 Jan 2023 through DLP.

Important Identified Risks

ARIA-E

A search was performed for events coded to the MedDRA PTs of Amyloid Related Imaging Abnormalities-oedema/effusion, brain oedema and vasogenic cerebral oedema during this period and cumulatively.

The majority of reports of ARIA-E were non-serious and asymptomatic. All reports of ARIA- E occurred prior to the 14th dose of lecanemab. Consistent with the description of symptomatic ARIA in the prescribing information, symptoms were generally mild to moderate with the most commonly reported symptoms being headache and confusion. Additional symptoms associated with ARIA included vision changes, dizziness/balance issues, memory loss and tiredness although more severe symptoms including focal neurological deficits and seizures have also been reported.

During the period there were 3 reports of deaths in patients who experienced ARIA-E, including 2 reports of concurrent ARIA-E and ARIA-H, all from spontaneous sources in the US. The reports of deaths in patients with ARIA-E occurred early in treatment, consistent with the expected timing of ARIA-E events, with 2 reports in *APOE4* carriers (1 homozygous carrier and 1 heterozygous carrier) and 1 where *APOE4* status was not known. Considering the estimated exposure there does not appear to be an increased risk relative to that observed in the clinical development programme. Additionally, the timing for these events was consistent with the timing observed for ARIA-E in general and there was no pattern, such as *APOE4* status or stage of disease at Leqembi initiation, to suggest a particular subgroup at increased risk. Details of these reports are summarised in Table 97 below.

Table 97. Reports of deaths in patients with ARIA-E during the report period

MFR Control No/Country/Source	Age	Gender	Reported Term(s)	Latency to Onset of Event	Comments
			Severe ARIA-H Microhaemorrhage Severe ARIA-E Moderate ARIA-H Superficial Siderosis Death	43 days	This healthcare professional report describes an *APOE4* heterozygous carrier who experienced symptomatic severe ARIA-E, severe ARIA-H (microhaemorrhage) and moderate superficial siderosis (reported symptoms included weakness, disorientation, unable to tell right from left, loss of appetite, problem with depth perception, unable to perform basic tasks, rash and confusion) approximately 1 month after starting Leqembi. One week later, the patient was hospitalised with status epilepticus. Leqembi was permanently discontinued, and the patient was treated with prednisone and levetiracetam with improvement in the seizures and the symptoms of ARIA. One month later, the patient was hospitalised for a second episode of status epilepticus, showed no improvement and was transitioned to hospice and passed away. The treating physician reported that the cause of death was not known but considered the death to be possibly related to Leqembi. It was unknown if an autopsy was performed. Past medical history was significant for, hyperlipidaemia, hypertension and past alcohol use. There was no history of seizures. Concomitant medications included simvastatin, fenofibrate and fish oil.
			Symptomatic ARIA-E Death	Unknown	This healthcare professional report describes a patient, *APOE4* status unknown, who experienced aphasia and left sided weakness after the 3rd dose of Leqembi. The patient was taken to the ER and confirmed to have experienced ARIA-E and was hospitalised. The action taken with Leqembi was not known. Nine days later, the patient died. The cause of death was not known. The outcome of ARIA-E at the time of death was ongoing. It was unknown if an autopsy was performed. Past medical history and concomitant medications were not provided.

MFR Control No/Country/Source	Age	Gender	Reported Term(s)	Latency to Onset of Event	Comments
			ARIA-E ARIA-H	36 days	This healthcare professional report describes an *APOE4* homozygous carrier who had confusion, memory loss and word finding difficulty following the 3rd dose of Leqembi. An MRI was performed, and the patient was diagnosed with ARIA-E and ARIA-H and Leqembi was discontinued. Two days later, the patient was hospitalised following a seizure and passed away 5 days later. An autopsy was not performed. Past medical history and concomitant medications were not provided.

ARIA-H (Cerebral Microhaemorrhage, Superficial Siderosis) and Intracerebral haemorrhage greater than 1 cm (i.e. Macrohaemorrhage)

A search was performed for events coded to the MedDRA PTs of amyloid related imaging abnormalities – microhaemorrhages and haemosiderin deposits, superficial siderosis of central nervous system, cerebral microhaemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhage intracranial, haemorrhagic cerebral infarction, haemorrhagic stroke and intraventricular haemorrhage during this period and cumulatively.

The majority of reports of ARIA-H (cerebral microhaemorrhage and superficial siderosis) were non-serious and asymptomatic. When symptoms were reported, the ARIA-H was generally concurrent with ARIA-E. There were no reports of ARIA-H in which the patient was concomitantly taking an anticoagulant.

In addition to the microhaemorrhages and superficial siderosis described above, during the reporting period there were 10 reports of cerebral haemorrhage (9 serious). Following the data lock point for the period, 1 report was noted to be a duplicate and has been invalidated. The size of the cerebral haemorrhage was confirmed to be > 1 cm for 2 of the reports. None of the reports of cerebral haemorrhage included the use of concomitant anticoagulants.

Two reports were consumer or office staff reports received via specialty pharmacies with a verbatim term of brain bleed or brain bleeding for which additional information was not available despite follow up attempts. There was also 1 report of brain bleed/ARIA/stroke without additional information regarding the final diagnosis despite follow up attempts. Additionally, there was 1 report of a patient who had an intraventricular haemorrhage and slight brain swelling following a fall which was described on MRI as mild brain swelling and possible small bleed. Due to the traumatic aetiology of the event, this report is unlikely to represent ICH related to Leqembi.

The remaining 5 reports include 1 fatal haemorrhagic stroke, which is discussed below. The other 4 reports are detailed in Table 98.

Table 98. Reports of cerebral haemorrhage during the report period

MFR Control No/Country/ Source	Age	Gender	Reported Term(s)	Latency to Onset of Event	Comments
			Intracerebral Haemorrhage (Parietal)	19 days	This physician report describes an *APOE4* non-carrier who had a headache on the day of each of the first 2 Leqembi infusions which resolved the following day. The patient had a CT scan on both occasions which revealed no abnormalities. Four days after the second infusion, the patient had a severe headache and fell, striking their head, and was noted to have altered mental status and right sided neglect. CT revealed an intracerebral haemorrhage in the parietal lobe and the patient was hospitalised. Leqembi was discontinued. The patient subsequently had a series of "mini strokes" and was transitioned to hospice. The reporter considered the intracerebral haemorrhage to be possibly related to Leqembi. Past medical history included a "couple" of microhaemorrhages, stroke 20 years earlier, a ministroke 9 months earlier, a head injury due to a motor vehicle accident. Concomitant medications included aspirin.
			ARIA-H (Intracerebral Haemorrhage, 1 cm or More)	28 days	This physician report describes an *APOE4* heterozygous carrier, who was found to have an ICH > 1 cm and concurrent ARIA-E on an MRI performed 27 days after initiating therapy with Leqembi. The intracerebral haemorrhage was classified as medically important by the treating physician. The patient was asymptomatic and did not require hospitalisation or other treatment. Leqembi was interrupted. Approximately 3 months later, the patient was recovering from the ICH and Leqembi was resumed. The patient was not taking any concomitant anti- thrombotic medications.
			ARIA-H (2cm)	29 days	This physician report describes an *APOE4* non-carrier who had a headache and decreased appetite over the course of the first month after starting treatment with Leqembi. An MRI was performed due to the presenting symptoms and the patient was diagnosed with a cerebral haemorrhage of 2 cm and the patient was hospitalised. The patient did not have concurrent ARIA-E. Leqembi was discontinued, and the event was not recovered. The patient did not receive any treatment for the event and was not taking any concomitant anti-thrombotics.
			One Small Haemorrhagic Stroke in Left Parietal Lobe Multiple Small Ischemic Strokes Multiple Microhaemorrhages	82 days	This physician report describes a patient, *APOE4* status unknown, who developed balance difficulties approximately 2 months after starting Leqembi. An MRI showed a small haemorrhagic stroke in the left parietal lobe, multiple small ischemic strokes and multiple microhaemorrhages, all of which were considered medically important by the reporter. Leqembi was interrupted. The outcome of the events was not recovered. The reporter considered the events to be probably related to Leqembi. Past medical history and concomitant medications were not known.

During the period there were 3 reports of deaths in patients who experienced ARIA-H or cerebral haemorrhage, all from spontaneous sources in the US. The 2 reports of concurrent ARIA-E and ARIA-H are detailed above ARIA-E and the third report is detailed below:

This spontaneous healthcare professional report describes a [redacted] *APOE4* non-carrier who received Leqembi for nearly a year. During that period, the patient had multiple MRIs without ARIA-E or ARIA-H. The patient was hospitalised for a large left parietal and occipital haemorrhagic stroke with 3 mm midline shift. Leqembi and co-suspect medications donepezil, memantine and buspirone were discontinued. The patient died due to the haemorrhagic stroke. An autopsy was not performed. The reporter considered the event to be possibly related to Leqembi. Past medical history was significant for cerebrovascular brain disease, chronic kidney disease stage 3, depression, anxiety, former smoker and transient ischaemic attack. Concomitant medications included modafinil, aspirin and tolterodine.

ARIA, including ARIA-H and intracerebral haemorrhage, is noted in the product information in the warning and precautions section, which indicates lecanemab, like other monoclonal antibodies targeting aggregated forms of Aβ, can cause ARIA, including ARIA-H. ARIA-H can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. These events usually occur early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. The prescribing information also notes that additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with lecanemab. Additionally, the prescribing information includes instructions on monitoring and management of ARIA, including treatment interruption.

This evaluation does not support an update of the characterisation of the important identified risk of ARIA-H (cerebral microhaemorrhage, superficial siderosis) and intracerebral haemorrhage greater than 1 cm (i.e. macrohaemorrhage).

5.1.2.2. Proposal for a Controlled Access Programme (CAP)

Per GVP module XVI, CAPs are interventions that seek to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures; with such programs guided by a clear therapeutic need for a product based on its demonstrated benefit, the nature of the risk associated with treatment and the likelihood that the risks can be managed by such a programme.

Herein we provide an outline of a potential CAP for lecanemab, and we are committed to working with the EMA on the specific details for the CAP prior to implementation in the EU.

5.1.2.2.1. Overview

The proposed CAP will promote the safe and effective use of lecanemab by healthcare professionals (HCPs), with patients having to be entered into the CAP platform prior to initiation of treatment in Europe.

The CAP would require HCPs to log-on to the platform and answer a series of questions that are aligned with the approved SmPC. If a response to a question is not aligned with the approved SmPC (for example, a HCP selects that the patient is a homozygous apolipoprotein E4 variant [APOE4] carrier) an alert would pop up indicating that this is inconsistent with the SmPC and requests that the HCP consults the approved SmPC.

It would be mandatory that all fields are completed, otherwise appropriate warnings would appear, and the HCP will not be able to proceed to the point of submission of the registration form.

Each HCP will be registered separately before they are able to enrol patients in the CAP. Part of the HCP registration process will require an attestation from the HCP that they have been provided with, and understand, the Guide for Healthcare Professionals and the SmPC.

5.1.2.2.2. Data to be Collected in the Controlled Access Programme

The proposed information to be collected is in line with the CAP that has been implemented in other regulatory territories already.

Taking into consideration General Data Protection Regulation (GDPR) requirements, the applicant proposes the following data fields will (a) promote the safe and effective use of lecanemab, and (b) prevent off-label use.

The questions and the provided choices for responses for specific patient information will focus the HCP on the Indication and Contraindications for lecanemab and limits the amount of patient-level data collected to what is necessary for the safe and effective use of lecanemab.

The appropriate patient population at the time of planned lecanemab initiation is established via a question concerning the confirmation of amyloid pathology: "Is there confirmation of amyloid pathology?".

Consistent with limiting the personal data collected, the APOE4 questions are directed towards the need for testing: "Is Apolipoprotein E4 (APOE4) genotype known?" and whether or not the patient is homozygote (use outside of the approved indication), "If Apolipoprotein E4 (APOE4) genotype is known, is the patient APOE4 Homozygous?", rather than collecting the specific genotype.

The remainder of the questions collect information related to information contained in Section 4.3 of the SmPC (Contraindications), such as, "Has the patient had a recent (within one year) magnetic resonance imaging scan (MRI)?" and "Are there findings suggestive of cerebral amyloid angiopathy?". Additional questions regarding potential MRI findings

follow and for this series of questions, all response fields are closed, "yes" or "no", (i.e. not free text). There is also a question on anticoagulant use: "Will the patient continue on anticoagulant therapy?" with response fields of "yes" or "no".

If any of the responses are not consistent with the indication and contraindications in the SmPC, then the patient will not be eligible to receive lecanemab therapy.

5.1.2.2.3. Proposal for an all-patients EU study, registry-based

Every EU patient will be enrolled in the proposed registry that will quantify the incidence of known adverse reactions (including though not necessarily limited to ARIA-E, -H, and ICH>1 cm), characterise the severity of these adverse events in real world use, and evaluate the association between these adverse reactions and relevant covariates including but not limited to APOE4 genotypes. In addition, the registry will collect information on progression to next stage of Alzheimer's disease.

The applicant committed to work with the EMA on the design of this registry.

5.2. Assessment of the grounds for re-examination

The argumentation of the applicant based on the newly provided analyses –with the focus on a restricted patient population, i.e. non-carrier and heterozygous APOE4 carriers - can be followed and it is based on the following main points:

1. ARIA (ARIA-E and ARIA-H) has been well characterised for lecanemab in study 301 based on its incidence, radiographic severity, and timing during treatment as well as on its presentation as serious and symptomatic events, and adequate information for longer treatment duration has been provided from the long-term extension.
2. Risk factors for ARIA and ICH>1 cm have been identified to inform risk minimisation measures.
3. ARIA events rarely present as symptomatic, serious and life-threatening events without full / no resolution. Severe symptoms of ARIA-E and –H such seizures are rare.
4. ARIA does not appear to be associated with accelerated long-term progression due to the observed brain volume loss.
5. Postmarketing experience of up to 18 months is available and supports the safety as characterised in study 301 and the risk minimisation measures proposed.
6. The proposed pharmacovigilance activities and risk minimisation measures are considered extensive with management comprising radiographic and symptomatic events as indicated in the product information, healthcare professional guide and checklist, patient alert card, follow-up questionnaire, educational material and a Controlled Access Programme. An EU all-patients study, registry-based, to further characterise ARIA-E, -H and also ICH>1 cm, as well as effectiveness of RMMs, drug utilisation and longer-term outcomes is proposed.
7. Although efficacy per se is not part of the grounds for refusal, the applicant has also described concisely the demonstrated treatment effects observed with lecanemab and presented additional analyses to further support the statistically significant efficacy results. The following points are worth mentioning:
    a. Primary endpoint: Change from Baseline in CDR-SB at 18 Months
    b. Key secondary endpoints: ADAS-Cog14 and ADCS-MCI-ADL
    c. Responder/progressor and slowing in progression of the disease (or "time saved" according to the applicant) relative to PBO analyses

These issues are discussed in detail in the following sections.

As a preliminary note to the in-depth discussion of each of the points mentioned above, the proposal of restricting the indication to non-carriers and heterozygous APOE4 carriers, identified as a subgroup where the risk of ARIA is lower, is endorsed. In the context of a trial with statistically persuasive establishment of efficacy in the primary population but with risk-benefit unconvincing in the same population, and with reference to the Guideline on investigation of subgroups in confirmatory trials (EMA/CHMP/539146/2013), this approach can be followed for the following reasons:

- The ApoE4 genotype status is a well-known risk factor for Alzheimer's disease and for ARIA events in the untreated population, and subgroup analysis by ApoE4 status was pre-specified'

There is a biological rationale for the increased risk of ARIA events in the homozygotes, and there is a genetic dose-response;

- Efficacy analysis shows that the APOE4 homozygotes were not driving the significance of the overall results;
- The finding of APOE4 status as a risk factor for ARIA is replicated in the literature with other medicinal products targeting amyloid.

The pertinence to this subgroup is established based on a genetic test. The assay used in the 301 study is based on PCR, is described in the submission and appears adequate. APOE4 Tests are also available in the EU. The applicant has agreed to insert in the SmPC a recommendation that the ApoE4 genotype should be assessed by a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose, and that if the CE-marked IVD is not available, an alternative validated test should be used.

Homozygous APOE4 carriers

A recent study (Fortea et al., 2024) concluded that APOE4 homozygotes represent a genetic form of AD, suggesting the need for individualised prevention strategies, clinical trials and treatments. Their study provides evidence to propose APOE4 homozygotes as another form of genetically determined AD (ADAD), similar to early-onset autosomal dominant Alzheimer's disease (ADAD) and Down syndrome associated Alzheimer's disease (DSAD). A commentary (Xu et al 2024) agreed with the authors that reclassifying APOE4 homozygosity as a genetic form of Alzheimer's disease would have an important influence on the design of clinical trials. So far, APOE4 homozygotes have not been treated as a separate predefined treatment group in clinical trials. It is suggested that APOE4 status must be recognised as a crucial parameter in trial design, patient recruitment and data analysis, with APOE4 homozygotes and heterozygotes being clearly separated (Xu et al., 2024).

5.2.1. ARIA (ARIA-E and ARIA-H) has been well characterised for lecanemab in study 301 based on its incidence, radiographic severity, and timing during treatment as well as on its presentation as serious and symptomatic events, and adequate information for longer treatment duration has been provided from the long-term extension.

Literature data is in support of ARIA-E and ARIA-H mainly being asymptomatic, but very rarely also being severe (including seizures) and leading to death. Moreover, ARIA-E typically resolves within 6 months after discontinuation of anti-amyloid treatment, while ARIA-H is persisting on MRI. In one-fourth of patients, ARIA-E re-occurs after re-initiation of anti-amyloid treatment. While a dose effect appears demonstrated for ARIA-E, this is less clear for ARIA-H. It is well documented that ARIA in APOE4 homozygous carriers is more likely symptomatic and severe (Doran et al., 2024).

A summary of all available ARIA and ICH events from core study 301, in the overall population and separated by APOE4 genotype has been compiled in Table 99.

ARIA-E:

In APOE4 noncarriers and heterozygous APOE4 carriers, ARIA-E events occurred with an incidence of < 11% based on study 301 core (noncarriers: 5.4% and APOE4 heterozygous carriers: 10.9%); see Table 58. The incidence of ARIA-E in the OLE of study 301 was consistent with the core period: TEAEs of ARIA-E up to 36 months of treatment with lecanemab are not expected to exceed the incidence of events during 18 months of treatment remaining below 13% of patients, which reassures that ARIA-E more frequently occurs during the first months of treatment and its incidence does not increase with longer treatment duration (Table 60).

Radiographic severity of ARIA-E events was mainly mild or moderate and rated as severe in 3% of APOE4 noncarriers and heterozygous APOE4 carriers during the 18 months treatment period and severity slightly worsened over the 36 months period including the OLE data (9% of ARIA-E was rated as severe); see Table 61.

Data suggest that in addition to an increased incidence of ARIA-E and ARIA-H events in patients with increasing number of APOE4 alleles, the incidence of symptomatic events and recurrences also increase with the number of APOE4 alleles. However, the timing of onset and resolution of ARIA-E do not seem to be impacted by APOE4 status.

Serious ARIA-E:

In APOE4 noncarriers and heterozygous APOE4 carriers, serious ARIA-E events did not occur with an incidence of more than 0.5% based on the data from study 301 core (noncarriers: 0.7% and APOE4 heterozygous carriers: 0.4%). In line with the 18-month 301 core data, the incidence of serious ARIA-E with continuous treatment up to 36 months remained stable and similar between noncarriers and APOE4 heterozygous carriers.

Symptomatic ARIA-E:

In APOE4 noncarriers and heterozygous APOE4 carriers, the incidence of symptomatic ARIA-E events did not exceed 1.6% based on up to 18 months of treatment with lecanemab (similar for noncarriers and heterozygous carriers of APOE4); see Table 64. The incidence of symptomatic ARIA-E with continuous treatment up to 36 months remained stable and similar between noncarriers and APOE4 heterozygous carriers. The most common symptoms were headache, confusional state, dizziness, and nausea. The majority of symptomatic ARIA-E were mild or moderate for all genotypes. Severe symptomatic ARIA-E in the restricted patient population in 301 core occurred in 2 patients, both heterozygous APOE4 carriers, and involved aphasia and generalised tonic-clonic seizure. Distribution of severity remained overall consistent during 36 months of continuous treatment with 4 patients reporting severe symptomatic ARIA-E in addition to the core study (involving 3 heterozygous APOE4 carriers with seizures and one noncarrier without seizures).

ARIA-H:

It has been observed in the literature that the incidences of ARIA-E and ARIA-H are positively correlated, and patients with ARIA-E in particular have higher risk of developing ARIA-H (Doran et al., 2024).

In APOE4 noncarriers and heterozygous APOE4 carriers, ARIA-H events *overall* occurred with an incidence of ~13% based on study 301 core and were similar for noncarriers and APOE4 heterozygous carriers, while being twice as high as for placebo in the same population (6.8%). The incidence of *isolated ARIA-H* (irrespective of APOE4 genotype) was similar for placebo and lecanemab (6% and 8%). The difference between lecanemab and placebo for ARIA-H events therefore relates to a significant number of ARIA-H occurring concurrently with ARIA-E with lecanemab: In 62% of noncarriers and APOE4 heterozygous carriers with ARIA-H, the ARIA-H was isolated, while for 38% of noncarriers and APOE4 heterozygous carriers, the ARIA-H was concurrent with ARIA-E. ARIA-H concurrent with ARIA-E (like ARIA-E alone) generally occurs early in treatment with the majority of events (~90%) within the first 6 months; however, isolated ARIA-H can be observed across the treatment period (Figure 30 and Figure 31). Given that isolated ARIA-H can occur at any time during the treatment, vigilance is also needed after the first 6 months. The SmPC states that if a patient experiences symptoms suggestive of ARIA at any time during treatment, clinical evaluation should be performed including an MRI. This point is further discussed below under the header 6 of pharmacovigilance and risk minimisation.

The incidence of ARIA-H overall and for isolated ARIA-H with continuous lecanemab treatment up to 36 months in the OLE of study 301 was slightly higher as compared with the core period, which is thought to be due to placebo-treated patients in the 301 core being treated with lecanemab for the first time in the OLE. 19.3% of noncarriers and APOE4 heterozygous carriers reported ARIA-H with up to 36 months of treatment with lecanemab while ~ 35% of the overall ARIA-H events overlapped with ARIA-E.

Radiographic severity of overall (and isolated) ARIA-H events was mainly mild or moderate and rated as severe in 1.6% (0.3%) of APOE4 noncarriers and heterozygous APOE4 carriers during the 18 months treatment period and severity only slightly worsened over the 36 months period (2.5% of overall ARIA-H and 0.6% of isolated ARIA-H was rated as severe); see Table 71.

Serious ARIA-H:

Two serious ARIA-H events were reported in the 301 core study, one in an APOE4 noncarrier and the other in a homozygous APOE4 carriers. 7 additional ARIA-H SAEs were reported in the OLE. Based on the 301 core and OLE experience, serious AEs of ARIA-H were all concurrent with ARIA-E events and none resolved. 6 of 9 events were symptomatic (headache, confusion, gait disturbances and also severe seizure in a single patient). One SAE led to death (homozygous carrier of APOE4). 5 of 9 SAEs of ARIA-H occurred in homozygous carriers of APOE4. Thus, restricting the indication to noncarriers and heterozygous carriers of APOE4 is expected to reduce the risk of serious ARIA-H events during long-term treatment with lecanemab.

Symptomatic ARIA-H:

In APOE4 noncarriers and heterozygous APOE4 carriers, the incidence of symptomatic ARIA-H events did not exceed 0.8% based on up to 18 months of treatment with lecanemab (similar for noncarriers and heterozygous carriers of APOE4); see Table 73. Isolated ARIA-H was rarely symptomatic in the overall population, thus hampering any conclusion with regard to the APOE4 genotype. The incidence of symptomatic ARIA-H overall and isolated with continuous treatment up to 36 months remained roughly stable and similar between noncarriers and APOE4 heterozygous carriers. The majority of symptomatic ARIA-H in the LEC10-BW-Treated Period was concurrent with ARIA-E. The most common symptoms were headache, dizziness, and confusional state.

All symptomatic ARIA-H events were mild or moderate for all genotypes in study 301 core, and distribution of severity remained overall consistent during 36 months of continuous treatment with 2 patients reporting severe symptomatic ARIA-H concurrent with ARIA-E, both of them being homozygous for APOE4 (i.e. outside of the indication being evaluated at re-examination), and one of them reported a seizure.

Table 99. Summary of all ARIA rates reported in study 301 core (green: revised indication; red: excluded population)

	All patients on PBO (N=897) % (n)	**All patients on LEC (N=898)** % (n)	**APOE4 Noncarrier: PBO (N=286)** % (n)	**APOE4 Noncarrier: LEC (N=278)** % (n)	**APOE4 Carrier: PBO (N=611)** % (n)	**APOE4 Carrier: LEC (N=620)** % (n)	**APOE4 Heterozygous: PBO (N=478)** % (n)	**APOE4 Heterozygous: LEC (N=479)** % (n)	**APOE4 Non-Carrier and Heterozygous APOE4 carriers - PBO** % (n)	**APOE4 Non-Carrier and Heterozygous APOE4 carriers - LEC** % (n)	**APOE4 Homozygous: PBO (N=133)** % (n)	**APOE4 Homozygous: LEC (N=141)** % (n)
ARIA-E	1.7 (15/897)	12.6 (113/898)	0.3 (1/286)	5.4 (15/278)	2.3 (14/611)	15.8 (98/620)	1.9 (9/478)	10.9 (52/479)	1.3 (10/764)	8.9 (67/757)	3.8 (5/133)	32.6 (46/141)
Symptomatic ARIA-E	-	2.8 (25/898)	-	1.4 (4/278)	-	3.4 (21/620)	-	1.7 (8/479)	-	1.6 (12/757)	-	9.2 (13/141)
ARIA-E SAEs	-	0.8 (7/898)	-	0.7 (2/278)	-	0.8 (5/620)	-	0.4 (2/479)	-	0.5 (4/757)	-	2.1 (3/141)
Recurrent ARIA-E events	0.1 (1/897)	3.1 (28/898)	0 (0)	0.4 (1/278)			0 (0)	1.5 (7/479)			0.8 (1/133)	14.2 (20/141)
Total ARIA-H (concurrent and isolated)	8.9 (80/897)	16.9 (152/898)	3.8 (11/286)	11.5 (32/278)	11.3 (69/611)	19.4 (120/620)	8.6 (41/478)	13.8 (66/479)	6.8 (52/764)	12.9 (98/757)	22.1 (28/133)	39 (55/141)
Symptomatic ARIA-H*	0.2 (2/897)	1.2 11/898)	-	0.7 (2/278)	0.3 (2/611)	1.5 (9/620)	0.2 (1/478)	0.8 (4/479)	0.1 (1/764)	0.8 (6/757)	0.8 (1/133)	3.5 (5/141)
ARIA-H SAEs	-	0.2 (2/898)	-	0.4 (1/278)	-	0.5 (1/620)	-	-	-	0.1 (1/757)	-	0.7 (1/141)
Recurrent ARIA-H events	2.7 (24/897)	6.8 (61/898)	0.3 (1/286)	2.2 (6/278)			2.3 (11/478)	5.2 (25/479)			9 (12/133)	22 (31/141)
ICH[2] (incl. non TEAE)	0.2 (2/897) [1]	0.7 (6/898) [1]	0.3 (1/286)	0.4 (1/278)	0.2 (1/611) [1]	0.8 (5/620) [1]	0.2 (1/478) [1]	0.6 (3/479) [1]	0.3 (2/764)	0.5 (4/757)	-	1.4 (2/141)
Isolated ARIA-H[3]	7.7 (69/897)	8.7 (78/898)	3.5 (10/286)	7.9 (22/278)	9.7 (59/611)	9 (56/620)	7.3 (35/478)	8.1 (39/479)	5.9 (45/764)	8.1 (61/757)	18 (24/133)	12.1 (17/141)
Symptomatic isolated ARIA-H	0.2 (2/897)	0.2 (2/898)	-	-	0.3 (2/611)	0.3 (2/620)	0.2 (1/478)	0.4 (2/479)	0.1 (1/764)	0.3 (2/757)	0.8 (1/133)	-

*1. Includes one non-treatment emergent adverse event (non-TEAE) case in each treatment group: event occurred during study but > 30 days after discontinuing study medication; 2. ICH -Intracerebral haemorrhage (>1cm) or macrohaemorrhage; 3. ARIA-H in subjects who did not also experience ARIA-E at any time. *Overall and isolated*

In summary, the newly provided analyses focussing on APOE4 noncarriers and heterozygous carriers show that the incidences of overall ARIA-E (8.9%) and ARIA-H (12.9%) for lecanemab are lower as compared to homozygous APOE4 carriers (32.6% and 39%, respectively). Moreover, longer treatment duration is not expected to increase the incidences of ARIA-E, serious ARIA-E, and symptomatic ARIA-E, as events mainly occur during the first 6 months of treatment, which is reassuring. The radiographic severity of ARIA-E was severe in a minority of patients and the exclusion of homozygous APOE4 carriers is expected to further reduce severe ARIA, which in turn is expected to lower the risk of potentially serious and life-threatening events, e.g. seizures, ICH, and haemorrhagic stroke. Radiographic severity did not worsen with longer treatment duration.

When APOE4 homozygous carriers are excluded from the overall population based on the newly provided analyses, the incidence of ARIA-H in the remaining population of APOE4 noncarriers and heterozygous carriers is roughly in line with the background rate for ARIA-H in the placebo arms of clinical trials (8.6% - 13.6%; Honig et al., 2024). ARIA-H frequently co-occurs with ARIA-E and the incidence of ARIA-H events and radiographic severity slightly increased during longer treatment duration; isolated ARIA-H is expected to occur during the entire treatment period with lecanemab. Exclusion of APOE4 homozygous carriers from treatment with lecanemab was found to reduce the overall incidences of serious ARIA-H and symptomatic ARIA-H events (the majority of SAEs and symptomatic ARIA-H occurred in homozygous carriers of APOE4 during the OLE of 301).

Based on the aforementioned analyses by genotype up to 36 months of treatment with lecanemab and exclusion of the patient population with highest risk for adverse outcomes, ARIA events – including serious and symptomatic event - are considered to be sufficiently characterised with regard to incidences, timing, and radiographic severity in the proposed indication.

Of note, slight differences have been noted in the numbers of ARIA events for the overall population in the dossier for the re-examination procedure in comparison to the original data submission, which have been explained in the legends of the tables due to definitions of these events and do not impact the assessment.

Moreover, while in the open-label study 301 patients could also be treated with lecanemab subcutaneously, the safety data in the dossier of the applicant is solely based on lecanemab being administered as intravenous infusion the 301 core plus OLE data (when combined) and did not include patients with subcutaneous administration of lecanemab.

5.2.2. Risk factors for ARIA and ICH>1 cm have been identified to inform risk minimisation measures.

Patients with Alzheimer’s disease are considered to have several risk factors that predispose them for ARIA events or ICH >1 cm, i.e. higher age, APOE4 carrier status, a history of stroke or cerebral microhaemorrhages, antithrombotic/ anticoagulant use, and vascular risk factors. Therefore, determination of eligibility for treatment with lecanemab is crucial and proper risk minimisation needs to be applied.

The APOE4 allele increases the risk of developing Alzheimer’s disease while it also increases cerebral amyloid deposition in the blood vessel walls and blood brain barrier permeability, leading to increased risk for microhaemorrhages or oedema (i.e. ARIA-E and -H events). Even without anti-amyloid treatment, patients with the APOE4 allele have a higher risk of CAA and cerebral microhaemorrhages (Ulrich et al., 2018; Piazza et al., 2022), and CAA increases the risk of intracerebral haemorrhage. The risk generally increases with the number of copies of the APOE4 allele.

As delineated in the final CHMP assessment report for the initial procedure, SAG-N experts (meeting convened on 17 June 2024) agreed by consensus that there should be a contraindication for homozygous APOE4 carriers in view of the high risk of ARIA. Therefore, the grounds for refusal specifically point towards the increased risk in apolipoprotein E4 (APOE4) homozygote carriers.

The analyses provided for ARIA-E, ARIA-H, and ICH > 1 cm by individual genotype clearly demonstrate an increased incidence, radiographic severity, and risk for recurrence of ARIA with the number of APOE4 alleles. In addition, and based on the data in re-examination Table 99, homozygous APOE4 carriers were found almost 3-times as likely to suffer from total ARIA-E and ARIA-H events, and 5-times as likely to suffer from symptomatic ARIA-E and SAEs of ARIA-E compared to heterozygous APOE4 carriers. The incidence of ICH was found twice as high for homozygous carriers as compared to heterozygous carriers of APOE4.

Three seizures in the 301 core were reported in the lecanemab group and these were associated with ARIA. Two of the three patients were APOE4 homozygous.

Moreover, two of the three fatal events associated with ARIA-E, ARIA-H, or ICH > 1 cm in the 301 OLE involved homozygous APOE4 carriers. Events in these patients included stroke, seizures and intracerebral haemorrhage.

In addition, lecanemab dose has been identified as a risk factor for ARIA-E, especially in the homozygous population. While dose reduction could have been considered to address this safety issue, doses below 10 mg/kg did not demonstrate efficacy; therefore, the applicant considered dose reduction for homozygous subjects not feasible.

In summary, restriction of the indication to APOE4 noncarriers and heterozygous carriers of APOE4 adequately addresses the rather unfavourable safety profile in homozygous APOE4 carriers based on an increased incidence of serious, symptomatic, and even fatal ARIA and ICH events.

ARIA is a consequence of the presence of amyloid in cerebral blood vessels walls (cerebral amyloid angiopathy; CAA), which is mobilised due to binding of monoclonal antibodies like lecanemab.

A study of the Uniform Data Set of the National Institute on Aging-funded Alzheimer's Disease Center (National Institute on Aging and the Alzheimer's Association [NIA-AA]) system that aimed to identify clinical factors associated with the presence of severe CAA in subjects with pathologically confirmed AD found that approximately 73% of homozygous *APOE4* carriers in the study population had severe CAA compared to approximately 27% that had no CAA, and subjects with CAA were more likely to have intracerebral haemorrhage than subjects without CAA (9.3% vs 3.5%) (Ringman, et al., 2014).

There were two (of the three) death cases reported in the 301 OLE, which described similar intense perivascular inflammation and microvascular degeneration based on detailed neuropathological descriptions of active inflammation/ ARIA (subjects 1091-1052 and 1121-1001). These fatalities occurred in the presence of CAA and APOE4 homozygous genotype as risk factors, while subject 1121-1001 additionally received antithrombotic medication (tPA) for cerebrovascular accident (Solopova et al., 2023; Reish et al., 2023).

Patients with >4 microhaemorrhages (i.e. severe CAA) were excluded from lecanemab trials due to a severely increased risk for ARIA-E and ARIA-H. Section 4.3 of the SmPC accounts for this risk. The applicant had proposed excluding patients with MRI findings suggestive of severe Cerebral Amyloid Angiopathy (CAA), defined as >4 microhaemorrhages or an area of superficial siderosis on pre-treatment MRI. Upon request, the applicant has agreed to an amended contraindication with a more comprehensive definition of potential indicators of CAA, as follows "Pre-treatment MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema, or other findings, which are suggestive of cerebral amyloid angiopathy (CAA)".

Clinical studies did not show a clear increase in the risk of ARIA-E and ARIA-H when lecanemab was administered to patients taking concomitant anticoagulant and / or antiplatelet agents neither for the overall population nor for the different APOE4 genotypes. In patients treated with lecanemab concurrently with anticoagulants/ thrombolytics, no serious or symptomatic ARIA-H was reported from post-marketing experience. Notwithstanding, antithrombotic use is a significant risk factor for developing ARIA-H and ICH (macrohaemorrhages) (Doran et al., 2024). In line with this, there seems to be an increased risk of ICH>1 cm in subjects being treated with lecanemab concomitantly with an anticoagulant alone or combined with an antiplatelet medication or aspirin (2.6%; 2/78 patients) compared to placebo (0%). This is further substantiated by one death case in the OLE of study 301 in a patient (homozygous for APOE4 as an additional risk factor), who suffered from multiple ICH>1 cm after tissue plasminogen activator following a cerebrovascular accident. Therefore, the applicant proposes additional measures in the SmPC, including a warning in section 4.4 with regard to initiation of thrombolytics in patients treated with lecanemab and description of ICH in section 4.8, which is endorsed. Furthermore, upon request, the applicant included a contraindication for initiation of lecanemab in patients receiving ongoing anticoagulant therapy. This is proposed as a precaution taking into account that available data at present are scarce. Moreover, section 4.4 was amended to address the management of lecanemab in case of anticoagulants or thrombolytic medications to be administered in patients already treated, i.e. a dose pause should be considered. This is in line with the appropriate use recommendations for lecanemab in the literature (Cummings et al. 2023). Recurrence of ARIA in the overall population has been thoroughly assessed as part of the original procedure.

ARIA-E was observed in 13% (113/898) of patients treated with lecanemab, of which 85% (96/113) continued on lecanemab treatment with or without dose interruption. Among those that continued lecanemab, 29% (28/96) experienced a recurrence (second event) of ARIA-E. 4/96 (4.2%) of LEC10-BW treated subjects experienced a third occurrence. One patient experienced four episodes of ARIA-E. One-third of recurrent ARIA-E were symptomatic (12/28; see Table 4 in the Day 195 clinical AR and Table 57 in the CHMP AR). The risk of recurrence increased with the number of *APOE4* alleles, consistent with the generally increased risk of ARIA with the number of APOE4 alleles.

ARIA-H (with or without concurrent ARIA-E) was observed in 17% (152/898) of patients treated with lecanemab and 9% (80/897) of patients on placebo, of which 82% (125/152) and 80% (64/80) continued treatment respectively with or without dose interruption. Among those that continued, 46% (57/125) of patients treated with lecanemab and 38% (24/64) of patients on placebo experienced a recurrence of ARIA-H. Overall, recurrence of ARIA-H (irrespective of treatment interruption/ discontinuation) occurred in 61/898 of the lecanemab-treated patients. Recurrent ARIA-H was symptomatic in 13% of patients (8/61 patients with recurrent events; see Table 58 in the CHMP AR). Again, the risk of recurrence increased with the number of *APOE4* alleles, consistent with the generally increased risk of ARIA with the number of APOE4 alleles.

In 79 LEC10-BW –treated subjects, treatment-emergent ARIA-E or ARIA-H (microhaemorrhage or superficial siderosis) led to interruption of study treatment. 69 of 79 (87.3%) subjects re-initiated treatment with lecanemab. Of these, more than half (56.5%, 39/69) had additional treatment-emergent ARIA-E or ARIA-H (microhaemorrhage or superficial siderosis) after re-initiation of treatment.

The applicant provided new analyses as part of the responses to the grounds for re-examination on the impact of dose pauses on the (re-) occurrence of ARIA:

Based on study 201 core data, 4 of 46 subjects *with ARIA-E* events (who had to discontinue treatment as per the protocol) entered the OLE phase after a prolonged treatment interruption of ~40 months. 3 of the 4 patients (75%) experienced recurrent ARIA-E, two of them were heterozygous carriers of APOE4 and one was a homozygous carrier (contrasting the ARIA-E recurrence rate of 29% in study

301). Severity of these ARIA-E events was mild in the 201 core study and switched to either mild, moderate, or severe upon re-treatment in the OLE. All of the three patients had more than 1 ARIA event (either ARIA-E and/ or ARIA-H) upon re-treatment. All recurrent ARIA events were asymptomatic.

The time to onset of ARIA after retreatment was in line with the study data except for one patient, when ARIA in the OLE occurred ~2.5 years after retreatment with lecanemab.

Based on study 201 core data, 7 of 57 subjects *with ARIA-H* events (who had to discontinue treatment as per the protocol) entered the OLE phase after a prolonged treatment interruption of ~19.4 months. 2 of the 7 patients (28.6%) experienced recurrent ARIA-H, both carriers of APOE4 (contrasting the ARIA-H recurrence rate of 46% in study 301). Severity of ARIA-H events was mild in the core study and switched to either mild, moderate, or severe upon re-treatment in the OLE. One patient had more than 1 ARIA event (either ARIA-E and/ or ARIA-H) upon re-treatment. The recurrent ARIA-H events were asymptomatic. The time to onset of ARIA –H after retreatment was early in one patient and occurred 2 years after the treatment gap in the other patient.

To conclude, only few subjects entered the OLE of study 201 after having had an ARIA-E or –H event in the core study. Although, some patients had worsening of severity of these events and more than 1 recurrent event, the overall number is too low to draw firm conclusions on the impact of a dose pause on the risk for recurrent ARIA events based on these data.

Analyses of ARIA after dose pauses in the core study 301: Among the 113 (152) patients with ARIA-E (ARIA-H) there were 4 patients with a dose pause of ≥6 months due to the respective ARIA event. 2 of the 4 subjects (50%) experienced a recurrent ARIA-E or -H event.

Twelve out of 672 patients (1.8%) with lecanemab treatment in the 301 core period, who entered the OLE of 301 (i.e. patients with continuous treatment up to 36 months) had ARIA-E for the first time in the OLE. 70 of 672 patients (10.2%) with lecanemab treatment in the 301 core period, who entered the OLE of 301 had ARIA-H for the first time in the OLE. None of the 672 patients with lecanemab treatment in the 301 core period, who entered the OLE of 301 had ICH > 1 cm. These numbers have not been further explained, and it remains unclear, how many of the 672 lecanemab-treated patients transitioning to the OLE phase of study 301 already experienced an ARIA-E/ ARIA-H/ ICH event during the core study. While only very few subjects with continuous lecanemab treatment from 301 core had ARIA-E for the first time in study 301 OLE, more patients had ARIA-H for the first time after the first 18 months of treatment in the OLE. This is in line with the finding that ARIA-E occurs early while ARIA-H can occur any time during lecanemab treatment.

In summary, the full implications of ARIA with long term lecanemab use remains unknown at present. In order to further address this risk, an all-EU patients observational study is proposed (see 5.). Nevertheless, restriction of the patient population to noncarriers and heterozygous carriers of APOE4 is considered to reduce the risk of ARIA recurrence, as this depends on the number of APOE4 alleles. Together with the other RMMs in place, this is considered sufficient.

5.2.3. ARIA events rarely present as symptomatic, serious and life-threatening events without full / no resolution. Severe symptoms of ARIA-E and –H such seizures are rare.

Symptomatic ARIA events or ICH can occur with anti-amyloid monoclonal antibodies, including lecanemab and include in rare cases seizures, focal neurologic deficits, encephalopathy, ICH, and ischemic stroke (Reish et al., 2023; Jeong et al., 2022; Sims et al., 2023; Gibson et al., 2024).

Seizures

As indicated by the applicant, seizures may occur as a symptom of severe ARIA-E and ARIA-H in rare cases. In the placebo group, seizures rarely occurred and were mainly not associated with ARIA-E or-H except for a single patient, who had ARIA-E and –H concurrently with seizures despite absence of ARIA on the baseline MRI. In the lecanemab group, three seizure events occurred concurrently with ARIA events. The ARIA events in these patients resolved radiographically; one event resolved with sequelae of partial seizures with secondary generalisation. Two of the three patients with seizures and ARIA were homozygous for APOE4, one was heterozygous. Seizures were temporally associated with COVID-19 infection and diverticulitis in one patient with ARIA-H, with anticoagulation and a severe / symptomatic ARIA-E event in another patient, and with radiographically severe, symptomatic ARIA-E event in the third patient. Taking into account restriction of the indication to heterozygous and noncarriers of APOE4 in the newly proposed label and the further alignment of section 4.3 with the appropriate use recommendations for ongoing anticoagulant treatment, it is considered that the risk of severe ARIA events that could lead to seizures is significantly reduced.

During the LEC10-BW treated period the incidence of seizures with and without ARIA increased relative to the 301 core period. Eight additional patients were reported with seizures with concurrent ARIA during 301 OLE. All except for one patient were APOE4 carriers. 6 of the 8 subjects received placebo in the core study 301. Of note, study drug was permanently discontinued in all of these patients (in 5 patients due to the concurrent ARIA events).

ICH > 1 cm

As referenced by the applicant from Honig et al. (2024), the rate of ICH>1 cm in PBO arms of AD studies ranges from 0.4% – 1%. The safety database for Leqembi includes one severe event of ICH in LEC10-BW in a patient receiving a concomitant anticoagulation treatment (tPA)

The *incidence of ICH > 1 cm* in the 301 core study was highest in the homozygous APOE4 carriers (LEC 10 mg /kg BW: 1.4% versus 0 in the placebo group). In the now proposed patient population (noncarriers and heterozygous APOE4 carriers), 4 patients (0.5%) had TEAEs of ICH > 1 cm; thus, the incidence is considered to remain within the placebo rates from AD trials. Cumulatively, ICH > 1 cm in the whole LEC 10-BW Treated Period for noncarriers and APOE4 heterozygous carriers occurred in 8 patients (0.6%) and remained therefore within the 301 core incidence and background placebo rates from other AD trials. Likewise, clinical severity did not increase with cumulative exposure to lecanemab during the 301 OLE while the small numbers of events preclude firm conclusions. The majority of ICH > 1 cm events were ongoing. Two events of ICH > 1 cm were fatal, amongst them, one in a homozygous APOE4 carrier and one in a noncarrier (described below).

In summary, if APOE4 homozygous carriers are excluded from the overall population based on the newly provided analyses, the incidence of ICH > 1 cm in the remaining population of APOE4 noncarriers and heterozygous carriers is in line with the background rate for ICH in placebo arms of clinical trials (0.4% - 1%) over 18 months as reported by Honig et al. (2024).

Serious AEs of ICH > 1 cm were reported for 4 patients on lecanemab in the 301 core, while one of them was not considered as treatment-emergent due to a latency between discontinuation of lecanemab and the onset of the event. Two SAEs occurred in placebo-treated patients. There appears to be no correlation of serious ICH > 1 cm with concurrent ARIA-E or with APOE4 genotype. In the 301 OLE, three additional SAEs were reported. The overall number of SAEs in the core and OLE study was too small to draw firm conclusions.

Symptomatic events of ICH > 1 cm solely occurred in three patients in the 301 Core period and its incidence did not increase with treatment duration. Symptoms reported were dysarthria, hemiparesis, asthenia, speech disorder, behaviour disorder, headache, monoparesis and partial seizures.

Deaths concurrent with ARIA-E, -H, or ICH > 1 cm

While no fatal events associated with ARIA-E, -H, and ICH > 1 cm have been reported in the 301 core study, there were three deaths concurrent with these events in the 301 OLE:

- An *APOE4 noncarrier* with placebo in the core study; 3 microhaemorrhages on screening MRI; receiving aspirin 81 mg and apixaban anticoagulation for atrial fibrillation. After receiving LEC for ~4 months, the subject fell, and safety MRI showed left occipital macrohaemorrhage. Apixaban was interrupted, and the subject had a myocardial infarction treated with heparin bolus (later discontinued due to ICH). A brain-only autopsy after death revealed "*intracerebral haemorrhage, left occipital cortex with no morphologic evidence of amyloid angiopathy. Etiology was thought to be cerebral amyloid angiopathy (CAA); however, no amyloid was present in the vicinity of haemorrhage. Differential diagnoses included a potential side effect of lecanemab, CAA where amyloid was removed by lecanemab, a lingering effect of anticoagulation treatment, or a combination of these. Subarachnoid haemorrhage was also noted in the left occipital cortex, which was separate from the left occipital haemorrhage*". The cause of death noted in the autopsy was "*No cause of death was present within the brain. A terminal cardiopulmonary event is most probable*". This case is confounded by the subject's concomitant use of apixaban and aspirin for ongoing atrial fibrillation and by the multiple falls preceding the cerebral haemorrhage. Moreover, and not mentioned previously, the subject experienced a COVID-19 infection in the months prior to death. COVID-19 is considered an independent risk factor for ICH and might have contributed to the fatal outcome (Benger et al, 2020; Dixon et al., 2020; Liang et al., 2021; Pavlov et al., 2020).
- A patient, *homozygous APOE4 carrier*, with placebo in the core study; died following an emergency hospitalisation with neurological symptoms of sudden onset, including possible seizure, and with an extensive brain swelling and bleeding (Solopova et al., 2023); the patient had cerebral symptoms compatible with an acute stroke after the 3rd dose of lecanemab, but was determined not to be a candidate for tPA; subject was taking acetylsalicylic acid 325 mg and heparin 18 units/kg IV QH (for atrial fibrillation) prior to or during the events described; MRI was performed 2 days after the start of the events and showed radiographically moderate ARIA-E, being reported as severe in clinical severity (51 microhaemorrhages), serious (hospitalisation), symptomatic, and deemed related to study drug. ARIA-H was also reported as severe in clinical severity, serious (hospitalisation), symptomatic, and deemed related to study drug. IV heparin was discontinued and solumedrol was started. The patient died 5 days after the start of the event. After an autopsy, the cause of death was determined as atherosclerotic and hypertensive heart disease with a contribution of acute respiratory distress syndrome. Neuropathological findings included in addition to AD neuropathological change, CAA related inflammation (CAA-ri), and moderate to severe small vessel ischemic disease. Furthermore, "the microscopic sections revealed the gross petechial haemorrhages were due to acute cerebral vasculitis", consistent with ARIA, and which is attributed to the lecanemab treatment and consistent also with CAA; this was confirmed by a second review suggesting that lecanemab may have exacerbated the underlying CAA, leading to many haemorrhages and ultimately to death. The temporal relationship of the initial event following the 3rd dose of lecanemab suggests that lecanemab is possibly involved in the exacerbation of the CAA.
- A patient, *homozygous APOE4 carrier*, with placebo in the core study; a safety MRI prior to the first treatment with LEC in the OLE revealed no ARIA-E, microhaemorrhage, macrohaemorrhages, or superficial siderosis; the subject appeared to have had an occlusive left sided cerebrovascular accident after the 3rd (and last) dose of LEC, and was treated with tPA (Castellani, et al., 2023; Reish, et al., 2023). The patient had bilateral cerebral haemorrhage 8 minutes after tPA infusion; seizure activity was noted; the patient died several days later. The autopsy showed "*extensive multifocal intraparenchymal haemorrhages,*

cerebral amyloid angiopathy (CAA), 'high' AD neuropathologic changes, and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within the blood-vessel walls". Although, the investigator classified the event of cerebrovascular accident to be not related to study drug, the event of cerebral haemorrhage was classified to be related to lecanemab. In addition, the publication by Castellani et al. (2023) states that "the neuropathological examination in this case indicates the presence of a robust phagocytic response to anti-Aβ therapy that extends beyond protofibrils and includes phagocytosis of insoluble Aβ aggregates of CAA" suggesting that the action of lecanemab could be involved in the haemorrhagic event. Reish et al. (2023) suggest that the extensive number and variation in sizes of the cerebral haemorrhages in this patient would be unusual as a complication of tPA solely related to cerebrovascular amyloid. Therefore, although the applicant considered the event as not related to the study medication based on the fact that "*there have been reports of fatal large catastrophic intracerebral haemorrhages after tPA administration in patients with CAA in the absence of anti-amyloid therapy, and considering that there have been reports in the literature of vasculitis associated with cerebral amyloid angiopathy in the absence of anti-amyloid therapy*", the timing of the event does not allow to rule out a relation with lecanemab. This case illustrates the need for thrombolytics as acute treatment for potentially life-threatening conditions such as stroke, myocardial infarction, and pulmonary embolism, but also anticoagulation treatments in an elderly population with a high risk of CV events.

In summary, the three above mentioned fatalities in patients with ARIA-E, ARIA-H, and ICH > 1 cm during treatment with lecanemab depict some communalities: (1) all patients were first treated with lecanemab in the OLE period of study 301; (2) the fatal events occurred within the known time-to-onset of ARIA events in the 301 core period, i.e. within the first 4 months of treatment; (3) CAA was present at the time of death in all subjects, which is the most common risk factor for ICH; (4) all three patient were treated with antithrombotic medication at the time of the events (subject 1042-1017 with apixaban and heparin; subject 1091-1052 with ASA and heparin; subject 1121-1001 with tPA).

Therefore, while a contribution of lecanemab is highly likely, these cases demonstrate a rather worst-case scenario, which is considered to be mitigated by the newly proposed safety measures, i.e. exclusion of APOE4 homozygous carriers from the indication (2 of the 3 death cases involved APOE4 homozygous carriers), and a contraindication for patients with any pre-treatment MRI findings suggestive of CAA (see also 2. Risk factors for ARIA and ICH>1 cm for proposal of a CI on anticoagulant treatment). Reference is made to section 6. risk minimisation measures for further information.

For death cases reported in the context of ARIA and/or ICH in the postmarketing setting, reference is made to point 5. below.

5.2.4. ARIA appears not associated with accelerated long-term progression due to the observed brain volume loss.

The applicant has performed an evaluation of the long term consequences of ARIA.

Data from Study 301 Core (18 Months Placebo-Controlled Treatment) and Study 301 Open Label Extension (36 Months Total Treatment)

The 18 month data (placebo-controlled treatment) from the Study 301 core and the open label extension (36 months total treatment) were analysed for subjects that progressed beyond different thresholds of CDR-SB, based on whether or not they experienced ARIA over 18 months. The proportion of LEC10-BW subjects that progressed beyond 3 or more points on CDR-SB for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population was calculated and the 18-month data compared

to placebo. A threshold of 3.0 on the CDR-SB represents twice the PBO decline (1.66) reported in Study 301 Core. With the 18- and 36-month datasets, irrespective of threshold used, or whether the events evaluated are ARIA-E, -H or concurrent ARIA-E, -H, there is no evidence that subjects with these events have accelerated cognitive and functional decline compared to those without these events.

However, the interpretation of the analysis by occurrence of ARIA is difficult because ARIA is a post-randomisation event such that the comparison is not based on randomised groups. It also remains unclear whether the worsening occurred before or after the ARIA event. Hence, some uncertainty remains, that should be addressed in the postmarketing setting, in particular in the EU Lecanemab All-Patient Study, registry based.

Figure 70. Time to worsening of CDR-SB by 3.0 points for subjects with and without ARIA in LEC10-BW and PBO – study 301 core (mITT)

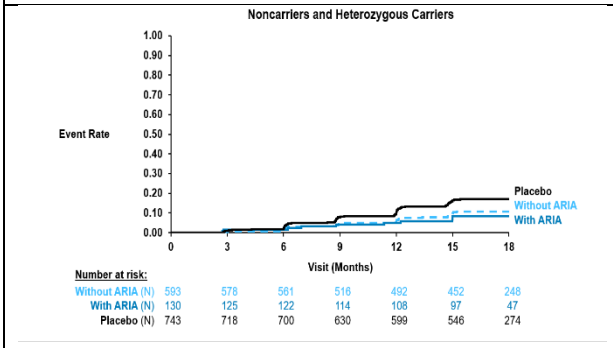
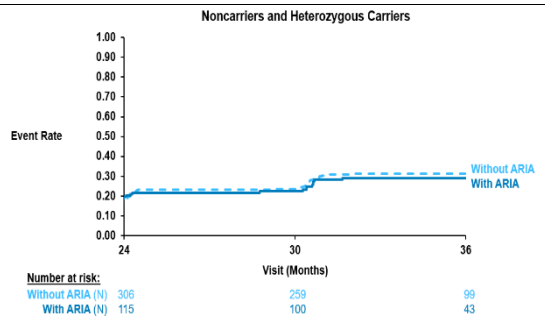


Figure 71. Time to worsening of CDR-SB by 3.0 points through 36 months for subjects with and without ARIA in LEC10-BW – study 301 core and OLE phase (mITT)



Time to worsening of CDR-SB scores is defined as time in days from randomisation to a confirmed worsening of the CDR-SB scores (i.e., the 1st worsening where there is an increase from baseline by at least 3.0 points on the CDR-SB score, in 2 consecutive visits). Time to worsening of CDR-SB scores will be censored at the date of last CDR assessment if no event. Time in months is calculated by time in days divided by 30.417.
APOE4 = apolipoprotein E4 variant, ARIA = amyloid-related imaging abnormalities, CDR-SB = Clinical Dementia Rating – Sum of Boxes, mITT = modified intent to treat, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.

Accelerated Brain Volume Loss (publications and Study 301 data)

Accelerated brain volume loss following anti-amyloid therapies for AD has been extensively discussed in the peer-reviewed Lancet Neurology publication by Belder, et al., 2024.

The relevant extracts (verbatim) from the publication are:

"*…trials of anti-amyloid monoclonal anti-bodies with successful amyloid removal have consistently shown excess brain volume changes of a magnitude less than 1% of brain volume. A reasonably consistent pattern of volume change has emerged, with proportionally greater excess volume change in the ventricular system than whole brain volume, and in the cortex compared with the brain as a whole. Importantly, there is no consistent evidence for excess hippocampal volume loss. Indeed, in trials showing slowing of cognitive decline, there was slight attenuation of hippocampal volume loss.*"

"*Given that therapies that induce the most amyloid clearance are associated with the greatest change in cerebral and ventricular volume, could the excess volume loss be explained by removal of amyloid β pathology? Although the total mass of amyloid β peptide in the brain of people with Alzheimer's disease has been estimated to be far less than is necessary to account for these volume changes, it is important to note that amyloid plaques occupy a volume much greater than that due to the amyloid β protein itself. Each plaque also contains a host of other proteins and dystrophic neurites, and is associated with reactive glia and fluid, all of which occupy volume.*"

The authors of the publication (Belder, et al., 2024) acknowledged that the cause of the paradoxical volume loss is not well understood, and has led to concerns that it might represent accelerated neurodegeneration and so lead to deleterious long-term outcomes. They looked at several anti-amyloid β immunotherapies for Alzheimer's disease: Solanezumab, Bapineuzumab, Gantenerumab, Lecanemab, Aducanumab, Donanemab and AN1792. They suggested that based on the current evidence, these changes can be best explained as amyloid-removal related pseudo-atrophy.

In another publication (Ten Kate, et al., 2024), analysis across all clinical studies of AD therapeutics demonstrate that across anti-amyloid therapies, brain volume loss appears to be related to the extent of amyloid removal, spares the hippocampus, and is not associated with worse clinical outcomes (at a group-level).

The findings from the lecanemab clinical programme are consistent with these publications. The data from the 36-month total treatment period from Study 301 show that greater brain volume loss is seen with more amyloid removal.

In conclusion, from the data of the Study 301 (18- and 36-month dataset) there is no evidence that subjects brain volume loss have accelerated cognitive and functional decline compared to those without these events.

For the proposed risk minimisation measures and additional pharmacovigilance for long-term consequences of ARIA, please refer to point 6. below.

5.2.5. Postmarketing experience of up to 18 months is available and supports the safety as characterised in study 301 and the risk minimisation measures proposed.

The applicant provided additional postmarketing safety data to aid to the understanding of transferability of ARIA and ICH occurrence and related symptomatology or clinical outcomes during study 301 (and its OLE) to the real-world patient population. The company's Global Safety Database (GSD) spans over 18 months from IBD on 6 January 2023 to 5 July 2024. However, exposure to lecanemab can only be estimated based on distributed vials and is given as 3125 patient-years. The known limitations of spontaneous reporting need to be considered. In addition to spontaneous reporting the applicant presented preliminary data from the postmarketing experience in Japan (collected in the postmarketing safety study BAN2401-J081-401). Up to 5 July 2024, ~2440 patients treated with lecanemab had been enrolled. However, the relevance of the Japanese data is considered very limited taking into account the indication sought in the EU, due to limited access to genotype testing for APOE4 in Japan and due to possible ethnic differences in susceptibility to ARIA (Toda et al., 2024; De Kort et al., 2024).

ARIA-E/ Serious ARIA-E/ Symptomatic ARIA-E

101 events of ARIA-E with detailed information have been reported in the GSD. Of these, 1/3 (25 events) were serious and ~40% were symptomatic events and all occurred prior to the 14th dose. Radiographic severity was unknown in 2/3 of cases but in line with the clinical study data for the reported events. In a majority of the events with known action, lecanemab was either interrupted or withdrawn. When APOE4 status was reported, the majority of events related to APOE4 carriers.

The serious events were mainly symptomatic (mostly headache, confusion; but also seizures have been reported). Serious ARIA-E was solely reported in APOE4 carriers. Three fatal events involved ARIA-E events, 2 of which were concurrent with ARIA-H. Regarding symptomatic ARIA-E in the GSD, the symptoms were in line with those described in study 301. Most of the symptomatic ARIA-E events involved homozygous APOE4 carriers.

The overall incidence of ARIA-E in the Japanese postmarketing setting was unexpectedly low (1.1%), with the vast majority of the events being nonserious, asymptomatic, and mild to moderate in severity. The incidences of serious ARIA-E and symptomatic ARIA-E events were consistent with study 301 Core (serious ARIA-E: 0.2% and 0.8%; symptomatic ARIA-E: 0.2% and 2.8%). Serious events were mainly symptomatic and vice versa (symptomatic events were mainly serious) and involved headache, confusion; but also seizures. All ARIA-E events occurred within the first 12 weeks of treatment.

ARIA-H/ Serious ARIA-H/ Symptomatic ARIA-H

100 events of ARIA-H have been reported in the *GSD*. Of these, 15% were serious ARIA-H events and 26% were symptomatic (mainly headache, confusion, but also seizures have been reported) and time to onset was within the first 6 months of treatment. More than half of the events occurred concurrently with ARIA-E. Radiographic severity was unknown in half of cases but in line with the clinical study data for the reported events (mainly mild to moderate). In a majority of the events with known action, lecanemab was either interrupted or withdrawn. When APOE4 status was reported, the majority of events related to APOE4 carriers. In 11% of the ARIA-H cases, antiplatelet agents were involved (no thrombolytics or anticoagulants).

The 15 serious events were mainly symptomatic (mostly headache, confusion; but also seizures have been reported) and concurrent with ARIA-E. Serious ARIA-E was solely reported in APOE4 carriers, when genotype status was known. In two patients with serious ARIA-H, the event was fatal and concurrent with ARIA-E. A majority of the 26 reported symptomatic ARIA-H events were concurrent with ARIA-E.

The overall incidence of ARIA-H in the Japanese postmarketing setting was 0.9%, far below the 17.3% in the 301 core study, all were nonserious, all but one were asymptomatic, and mild to moderate in severity, except for a single event that was severe. Time to onset was early in treatment (within 3 months) and half of the overall events were concurrent with ARIA-E (all symptomatic ARIA-H events were concurrent with ARIA-E).

Seizures with ARIA-E and/or ARIA-H

7 of 15 events of seizures reported in the *GSD* occurred in patients with ARIA events (either with or without concurrent ARIA-H). 2 of the 7 seizure events were fatal and reported in patients with concurrent ARIA-E and ARIA-H. However, no detailed information is available for these cases.

There was a single report of seizure associated with ARIA-E in the Japanese postmarketing setting.

ICH > 1 cm

12 events of ICH > 1 cm have been reported in the *GSD*. 8 events were not considered for further evaluation either due to a lack of information or with aetiology not related to lecanemab (fall). Three of the 12 events have been presented in more detail, all of them occurring within 2 months of treatment initiation; one of these events was finally probably related to lecanemab.

Three reports of ICH were obtained from the Japanese postmarketing setting, with two of them presented by the applicant: one AE of ICH was asymptomatic and concurrent with ARIA-E on an MRI; the other ICH event was not associated with ARIA-E. Both events occurred within one month of treatment initiation and none of these events involved antithrombotics.

Deaths with ARIA-E, ARIA-H, or ICH > 1 cm

Three fatal events involving ARIA-E and/or ARIA-H have been reported in the *GSD*. Of these, one patient was homozygous for APOE4, one was heterozygous for APOE4, and one was of unknown genotype.

Of these, two had ARIA-H concurrent with ARIA-E, and these patients had seizures prior to death (one patient with status epilepticus). One patient had ARIA-E while the cause of death remains unknown. All three fatal cases occurred within the time to onset of ARIA events (in the first three months of treatment). No autopsy results are available for these fatalities. Past medical history and concomitant medication was reported for a single case only, for which a contribution of lecanemab was considered possible.

One fatal event involving ICH > 1 cm in a noncarrier of APOE4 has been reported in the *GSD*. This patient was not reported with ARIA-E or ARIA-H over a year of treatment with lecanemab and died due to a haemorrhagic stroke, which was considered as possibly related to lecanemab, while an autopsy was not performed. The patient was reported with co-suspect medication (donepezil, memantine, and buspirone), and a medical history of cerebrovascular brain disease, TIA and smoking.

Ischemic stroke

Another case report involving a patient, heterozygous carrier of APOE4, with ischemic strokes and electrographic seizures in the setting of ARIA with lecanemab treatment was identified. The patient developed symptoms within the usual time-to-onset of ARIA events with lecanemab, i.e. after the 3rd infusion, consistent with severe ARIA-E and mild ARIA-H, and also restricted diffusion consistent with ischemic stroke. An EEG revealed focal seizures without clinical correlate; but an impaired cognitive and functional status. Antiplatelet treatment was commenced and stopped again due to new microhaemorrhages. The subject was treated with corticosteroids, lecanemab was stopped. The subject experienced further microhaemorrhages upon repeated MRI measures and ischemic stroke, and several episodes of confusion ~ 5 months after stopping lecanemab. Confusion was attributed to subclinical seizures and treatment with levetiracetam was commenced. The ischemic strokes were attributed to thrombosis in the setting of vessel wall inflammation due to amyloid plaque clearance in line with CAA-ri. The authors recommend that EEG monitoring should routinely be considered for patients with ARIA (Gibson et al., 2024).

In summary, the applicant provided data from postmarketing experience with lecanemab. The GSD covers up to 18 months of exposure to treatment with lecanemab from IBD to 5 July 2024, while for the Japanese postmarketing data, 2440 patients have been enrolled from September 2023 (approval of lecanemab in Japan) up to the data cut-off. While events from the spontaneous reporting and solicited reports from the GSD appeared to be increased over the experience in the clinical studies, it needs to be considered that exposure to lecanemab can only be estimated from the GSD. Based on the reported data, the time-to-onset and severity of events, the involvement of APOE4 carriers in these events, the concurrent appearance of ARIA-H with ARIA-E events in a majority of cases, and the symptoms reported (including seizures) are basically in line with the clinical study data. Of note, when action with treatment was reported, a majority of patients interrupted or discontinued lecanemab. This is considered to be covered by the recommendations based on the MRI outcomes given in the SmPC in section 4.2 . The overall incidences of ARIA events in the Japanese observational study were lower as compared to study 301 core. The relevance of this data is very limited for the indication sought in the EU, for reasons including the limited APOE4 genotyping and hypotheses - subject to scientific debate - with regard to ethnic differences in susceptibility to ARIA (Toda et al., 2024; De Kort et al., 2024). Postmarketing data contribute to the finding that seizures sometimes occur in patients presenting with ARIA and lecanemab treatment. Events of ICH have likewise been reported in the postmarketing setting but background information is scarce; one event was fatal (without previous ARIA event). In total, four death cases with ARIA and/or ICH have been reported postmarketing, with seizures preceding the fatal events but lacking a genotype pattern. It needs to be considered that information of the postmarketing fatal events is scarce and due to the uncontrolled setting cannot reliably be assessed.

5.2.6. The proposed pharmacovigilance activities and risk minimisation measures are considered extensive with management comprising radiographic and symptomatic events as indicated in the product information, healthcare professional guide and checklist, patient alert card, follow-up questionnaire, educational material and a Controlled Access Programme. An EU all-patients study, registry-based, to further characterise ARIA-E, -H and also ICH>1 cm, as well as effectiveness of RMMs, drug utilisation and longer term outcomes is proposed.

ARIA-E, ARIA-H and ICH > 1 cm are considered manageable by routine MRI monitoring after a baseline MRI. Data in the above sections 1. to 5. do not support that the restricted patient population is set at an unacceptably high risk for ARIA and ICH with the following RMMs taken into account.

The timing of monitoring, the consequences of ARIA and/ or ICH > 1 cm findings on MRI (dose suspension, discontinuation of treatment), follow-up measures, risk factors for ARIA/ICH, contraindications, etc. is part of the routine risk communication in the SmPC that has been further amended and refined as part of the re-examination to address the restricted patient population. SmPC section 4.2 covers MRI monitoring and frequencies, MRI follow-up, dosing suspension, discontinuation. SmPC section 4.3 covers contraindications in addition to the restriction of the indication in SmPC section 4.1. to heterozygous carriers and noncarriers of APOE4. These include patients with pre-treatment MRI findings in line with CAA, and patients with bleeding disorders that are not under adequate control. Moreover, SmPC section 4.4 includes detailed description of ARIA and its associated symptoms (if symptomatic); monitoring for ARIA (baseline, periodic, and follow-up MRIs); vigilance during the first 14 weeks of treatment; radiographic findings (severity); APOE4 Carrier Status and Risk of ARIA; and risk factors (concomitant antithrombotic medication, CAA).

Monitoring recommendations and warning statements are in line with the *Appropriate use recommendations (AUR*) for the treatment with lecanemab established by the Alzheimer's disease and Related Disorders Therapeutics Work Group to provide HCPs with detailed information on the safe use in clinical practice (Cummings et al., 2023). These AUR are informed by the inclusion and exclusion criteria applied in study 301 and provide recommendations for monitoring and management of ARIA.

Moreover, the applicant's proposal is now to restrict the indication in order to exclude homozygous APOE4 carriers from treatment with lecanemab given that they are at highest risk for symptomatic and severe ARIA as well as for recurrent events. This is considered appropriate for mitigating the risk of severe and symptomatic ARIA for patients treated with lecanemab in clinical practice.

During the procedure, the applicant has introduced several further revisions to the SmPC in response to Agency's request. This includes:

Section 4.2 informs on the need for a baseline MRI (within 6 months prior to treatment) as well as for regular MRIs prior to the 5th, 7th and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed including an MRI (see section 4.4).

Based on the data on radiographic severity of ARIA provided by the applicant for the intended population (noncarriers and heterozygous carriers of APOE4):

Lecanemab might be **continued** in the following situations:

- Asymptomatic, mild radiographic ARIA-E events
- Asymptomatic, mild radiographic ARIA-H events

Lecanemab should be **interrupted** in the following situations:

- symptomatic or radiographically moderate or severe ARIA-E; a follow-up MRI 2 to 4 months after initial identification should be conducted to confirm radiographic resolution;
- symptomatic mild or moderate or radiographically moderate ARIA-H; a follow-up MRI 2 to 4 months after initial identification should be conducted to confirm radiographic stabilisation;

Lecanemab should be **discontinued** in the following situations:

- after the second occurrence of symptomatic or radiographically moderate or severe ARIA-E
- radiographically or symptomatic severe ARIA-H
- intracerebral haemorrhage greater than 1 cm in diameter

Instructions for treatment interruptions and discontinuations would also be in lie with the appropriate use recommendations for lecanemab by Cummings et al. (2023)

Section 4.3 includes a contraindication for patients with bleeding disorders that are not under adequate control (an exclusion criterion in study 301) as well as patients with MRI findings suggestive of severe Cerebral Amyloid Angiopathy (CAA), defined as >4 microhaemorrhages or an area of superficial siderosis on pre-treatment MRI. Moreover, in the core study 301, ~10% of patients on lecanemab received concomitant anticoagulant treatment at baseline. In line with the AUR, it is proposed to also include a contraindication for patients receiving ongoing anticoagulant treatment, given that these patients are at an increased risk for macrohaemorrhage.

Risk factors for ARIA and ICH > 1 cm have been detailed in section 4.4 of the SmPC, including APOE4 carrier status, anticoagulants and thrombolytic medication, and the presence of an APOE4 allele that is associated with CAA while increasing the risk for ICH.

As ARIA-E and ARIA-H were considered not fully characterised, with uncertain long-term safety additional risk minimisation measures (HCP Educational Material and patient's EM – Patient Alert Card) were required and subsequently proposed by the applicant and agreed by the CHMP. The educational programme is aimed at all physicians prior to prescription of lecanemab. An ARIA Healthcare Professional Guide, and a Prescriber Checklist were proposed to be implemented for the important identified risks for lecanemab in the submitted RMP.

The Healthcare Professional Guide and Checklist reinforces the measures delineated in the SmPC and includes the need for handing out the PIL and patient alert card to the patient, clarifying information on ARIA and ICH, i.e. identification and management and risks (e.g. due to concomitant anticoagulants), and a list of tests to be conducted prior to prescription.

The patient alert card includes a request to read the PIL, and detailed information on ARIA symptoms and MRI monitoring during treatment with lecanemab and importance to seek medical advice for signs and symptoms of ARIA.

The applicant is also prepared to offer additional educational materials/ programmes for ARIA for other health care providers (e.g. radiologists, infusion nurses), which are not part of the RMP. This is endorsed in order to further raise the awareness on the risks associated with anti-amyloid (and specifically lecanemab) treatment. One of these programmes involves trainings on ARIA and CAA for radiologists by experienced neuroradiologists that were involved in study 301. Training material currently used in the US is in place for distribution in the EU, and includes general AD background information as well as detailed information on ARIA. Moreover, an independent ARIA educational website (www.ariaeducation.eu) will be developed to contain educational material around ARIA including interactive case review (a collaboration of academics and professional societies).

The Controlled Access Programme proposed will ensure that the medicine is exclusively used when all the RMMs are in place.

A PASS study has already been proposed in the original procedure. The newly proposed EU Lecanemab All-Patient Study, registry-based, will allow to precisely quantify the incidence of the main adverse effects of interest and to minimise the uncertainty around the very long-term effect of ARIA on disease progression. The study is considered key to the benefit-risk (PASS cat. 1).

In addition, to further characterise the important potential risk "acceleration of disease progression due to ARIA induced brain atrophy," the applicant has proposed to provide data from ongoing studies Study 301 OLE Phase and Study 303.

- Study 301 OLE Phase is an open-label study in individuals with early AD, as 31 Mar 2024, 464 subjects have been treated for ≥36 months.
- Study 303 is a 4-year study in individuals with preclinical AD and given the long duration of a PBO control (4 years), the applicant proposes to use this study characterise this important potential risk as described in the current RMP. As of 30 Apr 2024, 1168 subjects have been randomised.

In summary, the proposed pharmacovigilance activities in the product information as well as the postmarketing measures are considered extensive and appropriate to address the risk of ARIA and ICH with lecanemab treatment after exclusion of the homozygous APOE4 carriers, the patient population at highest risk for severe outcomes.

Moreover, the proposals for risk minimisation measures and additional pharmacovigilance by the applicant will be able to provide additional information for the extensively explored long term consequences of ARIA and brain volume differences.

5.2.7. Although efficacy per se is not part of the grounds for refusal, the applicant has also described concisely the demonstrated treatment effects observed with lecanemab and presented additional analyses to further support the statistically significant efficacy results.

Lecanemab was developed to slow the progression of AD in patients who are at the earliest symptomatic stages. There is a pharmacological rationale to intervene whilst patients are at the earliest symptomatic stages (MCI due to AD, mild AD).

The analysis for the primary endpoint of the pivotal study, using a control based imputation, showed for the overall population a statistically significant difference of -0.401 (95%CI -0.622, -0.180) between lecanemab and placebo in change from baseline in CDR-SB at 18 months.

Additionally, the 3 key clinical endpoints showed for the overall population statistically significant differences in favour of lecanemab versus placebo: -1.442 (95%CI: -2.270, -0.613; p=0.00065) in change from baseline in ADAS-Cog14 at 18 months, -0.050 (95%CI: -0.074, -0.027; p=0.00002) in change from baseline in ADACOMS at 18 months, and 2.016 (95% CI; 1.208, 2.823; p<0.00001) in change from baseline in ADCS MCI-ADL at 18 months.

These results are robust to violations of the assumptions on missingness as demonstrated in sensitivity analyses. Given the variety and nature of the endpoints, and the adequate design of the study, it is not credible that the effect can be attributed to unblinding or to other factors than the treatment.

As the indication being evaluated in the re-examination only includes patients who are non-carriers or heterozygotes (see above), the applicant has also provided several new post-hoc efficacy analyses for

the Noncarrier and Heterozygous *APOE4* Carrier subpopulation, to provide reassurance that the effect observed in the overall population was not driven by the subgroup that is now excluded. In fact, in the Noncarrier and Heterozygous *APOE4* Carrier subpopulation the treatment effect is nominally statistically significant and even numerically larger compared to the Overall population.

Moreover, long-term data suggests that the effect size, as measured by treatment difference on CDR-SB, appears to increase over time up until at least 36 months. However, it should be noted that beyond 18 months only indirect evidence supports this conclusion.

The following sections will focus mainly on the results for the Noncarrier and Heterozygous *APOE4* Carrier subpopulation.

a. Primary endpoint: Change from Baseline in CDR-SB at 18 and 36 Months

The CDR-SB scores (with higher scores indicating more impairment) are a reliable and accepted global tool for the evaluation of Alzheimer's disease patients.

For the Overall Population, the adjusted mean treatment difference between LEC10-BW and placebo in the change from baseline in CSR-SB at month 18 was statistically significant with -0.45 (95% CI: -0.669, -0.233) corresponding to 27.1% less decline with LEC10-BW compared to PBO, P=0.00005. This may be considered as a small but clear and statistically significant effect.

For the Noncarrier and Heterozygous APOE4 Carrier Population, the adjusted mean treatment difference was -0.58 (95% CI: -0.811, -0.347), corresponding to 33.5% less decline with LEC10-BW compared to PBO. The effect is numerically larger than that observed for the Overall population again providing reassurance that the effect is not driven by the homozygous population.

Sensitivity and supplementary analyses for CDR-SB were also statistically significant.

Table 100. Change from baseline in CDR-SB at 18 months – sensitivity and supplementary analyses – noncarrier and heterozygous APOE4 carrier population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference
MMRM with control-based imputation of missing data Analysis set = mITT	1.748	1.209	-0.538	(-0.774, -0.303)
MMRM on all randomised subjects[a]. Analysis set = Randomised Set	1.722	1.168	-0.554	(-0.777, -0.331)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1521) are included.

The comparison to an observational natural history cohort provides supportive data suggesting that the results seen at 18 months may be sustained through 36 months.

Study 301 Core and OLE Phase compared to natural disease progression through 36 months (ADNI).

An observational natural history cohort (Alzheimer's Disease Neuroimaging Initiative [ADNI]) of early AD patients was established prior to the start of Study 301.

The applicant used the ADNI cohort to design Study 301, selecting a priori a representative early AD observational cohort from ADNI. Of the ADNI cohort, the applicant used all 436 patients who met certain criteria. Throughout the development of lecanemab, the applicant has used data from the ADNI study to aid in decision-making for the programme (for example, for estimations of PBO decline to aid in power calculations).

The observational cohort criteria matched the planned key inclusion criteria and study population for Study 301:

(1) baseline diagnosis of "MCI" with global CDR = 0.5 and CDR memory ≥0.5 or baseline diagnosis of "AD" with global CDR = 0.5 or 1.0 and CDR memory ≥0.5

(2) proportion of MCI (60%) and mild AD (40%)

(3) baseline Mini-Mental State Examination (MMSE) ≥22

(4) at least 1 of 2 criteria for amyloid positivity

(4a) baseline amyloid PET SUVr florbetapir ≥1.11 or amyloid PET SUVr Pittsburgh compound B (PIB) ≥1.47 or

(4b) baseline cerebrospinal fluid (CSF) total tau/amyloid beta (Aβ)>0.222

The same patient cohort has been followed by ADNI for several years and the study continues (https://adni.loni.usc.edu/help-faqs/adni-documentation/). As it can be seen from the following table, the baseline demographic and clinical characteristics are similar between Study 301 Core and the pre-specified ADNI cohort.

Table 101. Baseline demographic and clinical characteristics – study 301 core and ADNI

Category	**Study 301 Combined Total (Lecanemab 10 mg/kg Biweekly and Placebo)**	**ADNI**
N	1795	436
Age		
Mean (SD)	71.3 (7.83)	73.8 (7.38)
Median	72.0	74.4
APOE4 Carrier Status		
Positive n (%)	1231 (**68.6**)	305 (**70.0)**
Negative n (%)	564 (**31.4**)	131 (**30.0**)
Disease Stage[a], n (%)		
MCI due to AD	1107 (61.7)	267 (61.2)
Mild AD	688 (**38.3**)	169 (**38.8**)
Baseline CDR-SB		
Mean (SD)	**3.20 (1.340)**	**2.66 (1.662)**
Median	3.00	2.50

AD = Alzheimer's disease, ADNI = Alzheimer's Disease Neuroimaging Initiative, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, LEC10 BW = lecanemab 10 mg/kg biweekly, MCI = mild cognitive impairment, OLE = open-label extension, PBO = placebo, SD = standard deviation. Age is calculated at date of informed consent in Core Study for Study 301 Core, and at enrolment for ADNI. a: Disease stage in Study 301 was collected at baseline in Core Study. Source: Study 301 Core CSR Tables 14.1.4.1.3, 14.1.4.1.6; ADNI 2020 data download.

A separation between the early start (subjects treated with LEC10-BW during the Core) and delayed start (subjects treated with PBO during the Core and subsequently treated with LEC10-BW in the OLE Phase) was maintained between 18 and 36 months when all subjects received LEC10-BW. The curves for the early start and delayed start between 18 to 36 months suggest parallel disease trajectories at least over a 36 month period. This suggests that the effect of lecanemab is not merely symptomatic.

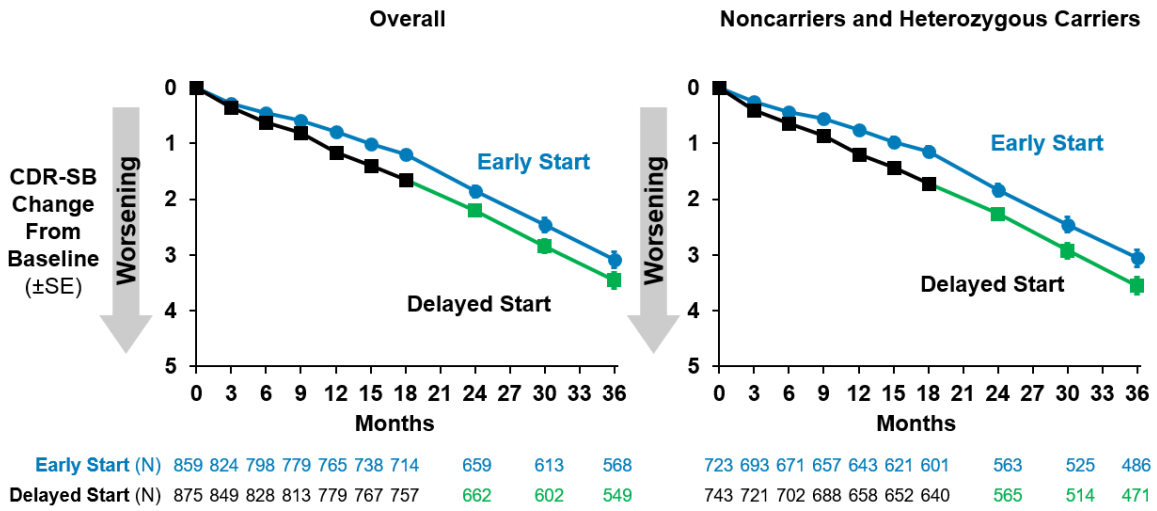


Figure 72. Adjusted mean change from baseline in CDR-SB through 36 months – study 301 core and OLE phase (mITT)

Since there is not a PBO group during the OLE phase of Study 301 between 18 and 36 months, this ADNI natural history cohort was used to assess the effect of long-term LEC10-BW treatment relative to the natural history of decline on CDR-SB.

The comparison of LEC10-BW with ADNI revealed the following:

For the Overall Population: At 36 months, the adjusted mean change from core study baseline in CDR-SB for LEC10-BW (3.087) was compared with the adjusted mean change from baseline in CDR-SB for the ADNI cohort (4.032). At 36 months, the adjusted mean treatment difference between LEC10-BW and the ADNI cohort was -0.95 corresponding to 7.6 months' delay in progression of the disease (or "time saved" according to the applicant's terminology).

In a similar manner and without formal statistical comparisons, for the Noncarrier and Heterozygous APOE4 Carrier Population: at 36 months the adjusted mean change from core study baseline in CDR-SB for LEC10-BW (3.060) was compared with the adjusted mean change from baseline in CDR-SB for the ADNI cohort (3.916). At 36 months, the adjusted mean treatment difference was -0.86 between LEC10-BW and the ADNI cohort corresponding to 6.8 months' delay in progression (or "time saved" according to the applicant), the difference being only slightly smaller for the overall population.

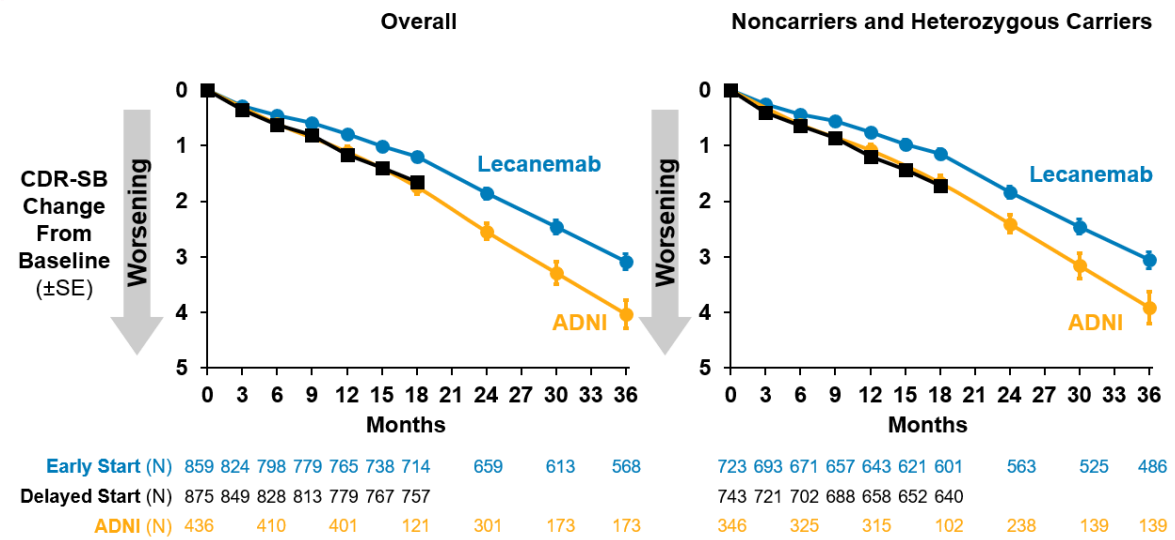


Figure 73. Adjusted mean change from baseline in CDR-SB in context of observational cohort through 36 months – study 301 core and OLE phase (mITT)

ADNI = Alzheimer's Disease Neuroimaging Initiative, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, mITT = modified intent to treat, OLE = open-label extension, SE = standard error. Includes intravenous and subcutaneous-treated subjects.

It should be noted that the data from the Study 301 Core have been generated with lecanemab 10mg/kg administered in approximately 60-minute intravenous infusions every two weeks (LEC10-BW). The study 301 OLE includes data from the substudies in which the weekly subcutaneous administration of lecanemab is also explored. Bioavailability data do not indicate that the route of administration has an impact on the interpretation of the efficacy data.

In conclusion, a small but statistically significant effect on the primary endpoint CDR-SB has already been demonstrated for the overall population at 18 months. Nominally statistically significant results were also obtained for the Noncarrier and Heterozygous APOE4 Carrier subpopulation at 18 months. For the 36 months analyses, clear differences over time were found in favour of LEC10-BW compared to the ADNI natural history cohort. This can be attributed to a faster deterioration in the untreated ADNI cohort. Even though these results were without formal statistical comparisons, they can support the findings of the primary analyses and are supportive of a continuous effect of lecanemab in slowing the progression of Alzheimer's disease.

The general limitations of non-randomised comparisons to external controls that may be subject to confounding should be taken into account. However, the decline in the placebo patients was comparable to the decline in the ADNI cohort for the duration of the placebo-controlled phase (18 months). According to the figures shown in Figure 73, missing data after 18 months was substantial both in the LEC10-BW patients and in the ADNI cohort with less than 50% of ADNI patients providing data after 36 months. Therefore, conclusions may strongly depend on the missing data assumptions and may not be fully robust.

However, all the findings are towards the same direction that there is treatment effect from lecanemab, which is maintained through to month 36.

b. Key secondary endpoints: ADAS-Cog14 and ADCS-MCI-ADL

ADAS-Cog14 at 18 months

For the Overall Population the adjusted mean treatment difference in the change from baseline for ADAS-Cog14 at 18 months was -1.44, corresponding to 25.8% less decline with LEC10-BW compared to PBO, P=0.00065.

For the Noncarrier and Heterozygous APOE4 Carrier Population the treatment difference **-1.63**, corresponding to 27.9% less decline with LEC10-BW compared to PBO, P=0.00052.

Sensitivity and supplementary analyses for ADAS-Cog14 were also statistically significant and produced similar values to the initial analysis.

Table 102. Change from baseline in ADAS-Cog14 at 18 months – sensitivity and supplementary analyses – noncarrier and heterozygous APOE4 carrier population

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline PBO	Adjusted mean change from baseline LEC10-BW	Adjusted mean difference	95% CI for difference	*P* value
MMRM with control-based imputation. Analysis set = mITT	5.907	4.330	-1.577	(-2.514, -0.640)	<0.001
MMRM on all randomised subjects[a]. Analysis set = Randomised Set	5.794	4.240	-1.554	(-2.436, -0.672)	<0.001

AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo. a: All randomised subjects (N=1521) are included. Source: Appendix 1 Table 14.2.2.2.41.7e and Appendix 1 Table 14.2.2.2.15nh.

ADAS-Cog14 at 36 months

An ADNI line was not provided for ADAS-Cog14 as this specific scale is not captured in the observational cohort. The comparison was therefore only performed between the early start (subjects treated with LEC10-BW during the Core) and delayed start (subjects treated with PBO during the Core and subsequently treated with LEC10-BW in the OLE Phase). The following figure presents the change from baseline for ADAS-Cog14 after 12 months and maintained up to 36 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. A clear separation between the early start and the delayed start (newly treated) was observed at week 157. The results for the overall population were adjusted mean difference: early start - delayed start -1.101, 95% Confidence interval for differences -2.520, 0.318, p-value 0.12811. For the Noncarrier and Heterozygous APOE4 Carrier Population there was an adjusted mean difference: early start - delayed start -1.564, 95% Confidence interval for differences -3.142, 0.015, p-value 0.05215. This, as in the case of CDR-SB, is also supportive of the maintenance of the treatment effect, which is indicative of a disease modifying effect. The difference between the early and the delayed start group remains, since the curves are not coming together.

For the Overall Population the adjusted mean treatment difference in the change from baseline for ADAS-Gog14 at 36 months was -1.10 between LEC10-BW early start and the delayed start.

In the case of the Noncarrier and Heterozygous APOE4 Carrier population, the adjusted mean treatment difference was -1.56 between LEC10-BW early start and the delayed start.

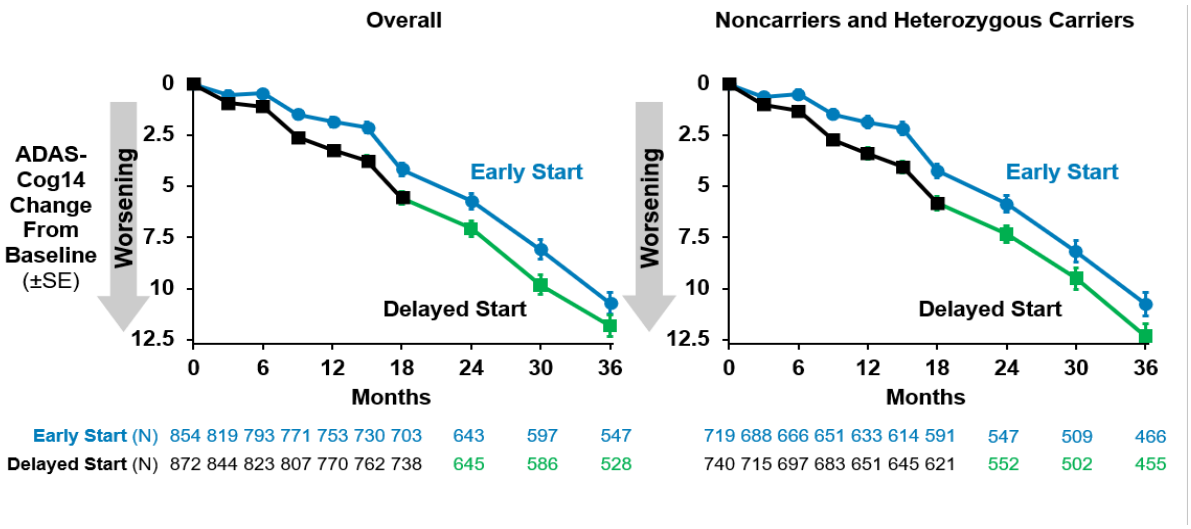


Figure 74. Adjusted mean change from baseline in ADAS-Cog14 through 36 months – study 301 core and OLE phase (mITT)

ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale 14-item version, *APOE4* = apolipoprotein E4, mITT = modified intent to treat, OLE = open-label extension, SE = standard error. Includes intravenous and subcutaneous-treated subjects.

ADCS-MCI-ADL at 18 months

For the Overall Population, the adjusted mean treatment difference in the change from baseline for ADCS-MCI-ADL at 18 months was 2.02, corresponding to 36.6% less decline with LEC10-BW compared to PBO, P<0.00001.

For the Noncarrier and Heterozygous APOE4 Carrier population, the adjusted mean treatment difference was 2.23, corresponding to 39.2% less decline with LEC10 BW compared to PBO, P<0.00001.

Sensitivity and supplementary analyses for ADCS-MCI-ADL were also statistically significant and similar to the initial analysis.

Table 103. Change from baseline in ADCS-MCI-ADL at 18 months – sensitivity and supplementary analyses – noncarrier and heterozygous APOE4 carrier population

Type of sensitivity or supplementary analysis	**Adjusted mean change from baseline PBO**	**Adjusted mean change from baseline LEC10-BW**	**Adjusted mean difference**	**95% CI for difference**	***P* value**
MMRM with control-based imputation Analysis set = mITT	-5.853	-3.839	2.014	(1.104, 2.924)	<0.001
MMRM on all randomised subjects[b] Analysis set = Randomised Set	-5.527	-3.581	1.947	(1.169, 2.724)	<0.001

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment, LEC10-BW = lecanemab 10 mg/kg biweekly, mITT = modified intent to treat, MMRM = mixed model for repeated measures, PBO = placebo.
a: All randomised subjects (N=1521) are included.

ADCS-MCI-ADL at 36 months

An ADNI line was not provided for ADCS-MCI-ADL, either, as this specific scale is not captured in the observational cohort. The following figure presents the change from baseline for ADCS-MCI-ADL at 36 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population. A similar pattern to that of ADAS-Cog14 with a separation from 12 months and maintained up to 36 months between early and delayed start lecanemab treatment was observed in this case as well, supportive of a maintenance of effect caused by a disease modifying treatment.

At week 157, the results for the overall population were adjusted mean difference: early start - delayed start 1.804, 95% Confidence interval for differences 0.504, 3.105, p-value 0.00659.

And for the Noncarrier and Heterozygous APOE4 Carrier Population there was an adjusted mean difference: early start - delayed start 1.799, 95% Confidence interval for differences 0.390, 3.207, p-value 0.01236.

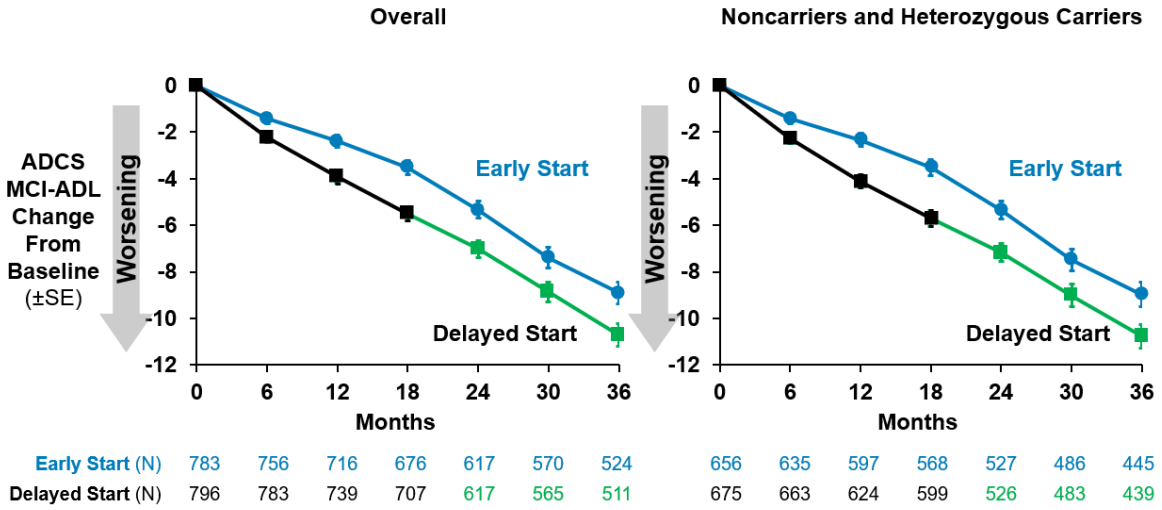


Figure 75. Adjusted mean change from baseline in ADCS-MCI-ADL – study 301 core and OLE phase (mITT) (36 months)

ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for use in Mild Cognitive Impairment, *APOE4* = apolipoprotein E4, mITT = modified intent to treat, OLE = open-label extension, SE = standard error. Includes intravenous and subcutaneous-treated subjects.

In the case of ADCS-MCI-ADL a clear treatment effect was observed at 36 months (or week 157) for the Noncarrier and Heterozygous APOE4 Carrier Population with an adjusted mean treatment difference was 1.80 between LEC10-BW early start and delayed start. This is clearly supportive of the primary endpoint findings and a robust demonstration of consistent results for a disease modifying treatment.

c. Responder/progressor and delay in progression (or "time saved" according to the applicant) relative to PBO analyses

In addition to the statistically significant results in the primary and key secondary endpoints at month 18 and the clear differences observed at month 36 between LEC10-BW and ADNI or between early- and delayed-start lecanemab treatment, the following analyses are considered as the supporting evidence of treatment effect by lecanemab by demonstrating slowing in disease progression together with the corresponding benefit for patients.

Further characterisation was therefore conducted by time to progression to clinically meaningful milestones and responder/progressor analyses in line with the AD guideline recommendations.

The global CDR score represents the following stages of disease: 0 = unimpaired; 0.5 = questionable impairment (MCI); 1, 2, 3 = mild, moderate, severe dementia respectively. The pre-specified (Overall Population) time to worsening of a global CDR score was defined as time from randomisation to the time of worsening of the global CDR score (i.e., the 1st worsening where there is an increase from baseline in global CDR on 2 consecutive visits by at least 0.5 points for MCI subjects [baseline global CDR 0.5] and by at least 1 point for mild AD subjects [baseline global CDR 1]). This analysis represents patients moving to the next stage of AD and it is therefore considered clinically meaningful.

The results presenting time to worsening of global CDR score at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population were consistent across both populations. The hazard ratio for the Overall population was 0.69 (95% CI: 0.57, 0.83, p=0.00011) and for the Noncarrier and Heterozygous *APOE4* Carrier Population this was 0.66 (95% CI: 0.53, 0.81).

Additional analyses presenting time to event analyses (event defined as decline by 0.5 and 2.0 on CDR-SB) at 18 months for the Overall Population and the Noncarrier and Heterozygous *APOE4* Carrier Population were also conducted. Similar to what was reported for the global CDR Score, statistically significant results were consistent across both populations with greater than 18% reduced risk of worsening by 0.5 and greater than 32% reduced risk of worsening by 2.0 on CDR-SB.

For the Overall Population:

- LEC10-BW reduced the hazard of worsening by 0.5 on CDR-SB by 18%. The HR of worsening is 0.820 (95% CI [0.727, 0.924], P=0.00116)
- LEC10-BW reduced the hazard of worsening by 2.0 on CDR-SB by 32%. The HR of worsening is 0.684 (95% CI [0.563, 0.832], P=0.00014)

For the Noncarrier and Heterozygous APOE4 Carrier Population post-hoc analyses:

- LEC10-BW reduced the hazard of worsening by 0.5 on CDR-SB by 22%. The HR of worsening is 0.782 (95% CI [0.687, 0.892], nominal P=0.00023)
- LEC10-BW reduced the hazard of worsening by 2.0 on CDR-SB by 37%. The HR of worsening is 0.634 (95% CI [0.513, 0.784], nominal P=0.00002)

Apparently, the favourable effect is not driven by the APOE4 homozygous and therefore we can rely on the overall estimate.

Progressor analyses to assess the proportion of subjects in PBO and LEC10-BW that progressed by increasing thresholds on the CDR-SB, ADAS-Cog14 and ADCS-MCI-ADL scales in Study 301 by 18 month were also performed, further supporting the results of the primary endpoint, key secondary endpoints and time to event analyses.

A 1.5-point decline on CDR-SB would generally reflect a subject deteriorating in more than one cognitive or functional CDR-SB domains. Progression by 1.5 or more on CDR-SB represents the median decline for PBO.

At this threshold:

- For the Overall Population, 50% of PBO subjects declined compared to 36% of LEC10-BW subjects, representing a 28% reduction in relative risk (in the progression by 1.5 or more on CDR SB which represents the median decline for PBO) (see following figure).

- For the Noncarrier and Heterozygous APOE4 Carrier Population 53% of PBO subjects declined compared to 35% of LEC10-BW subjects, representing a **34% reduction in relative risk**.

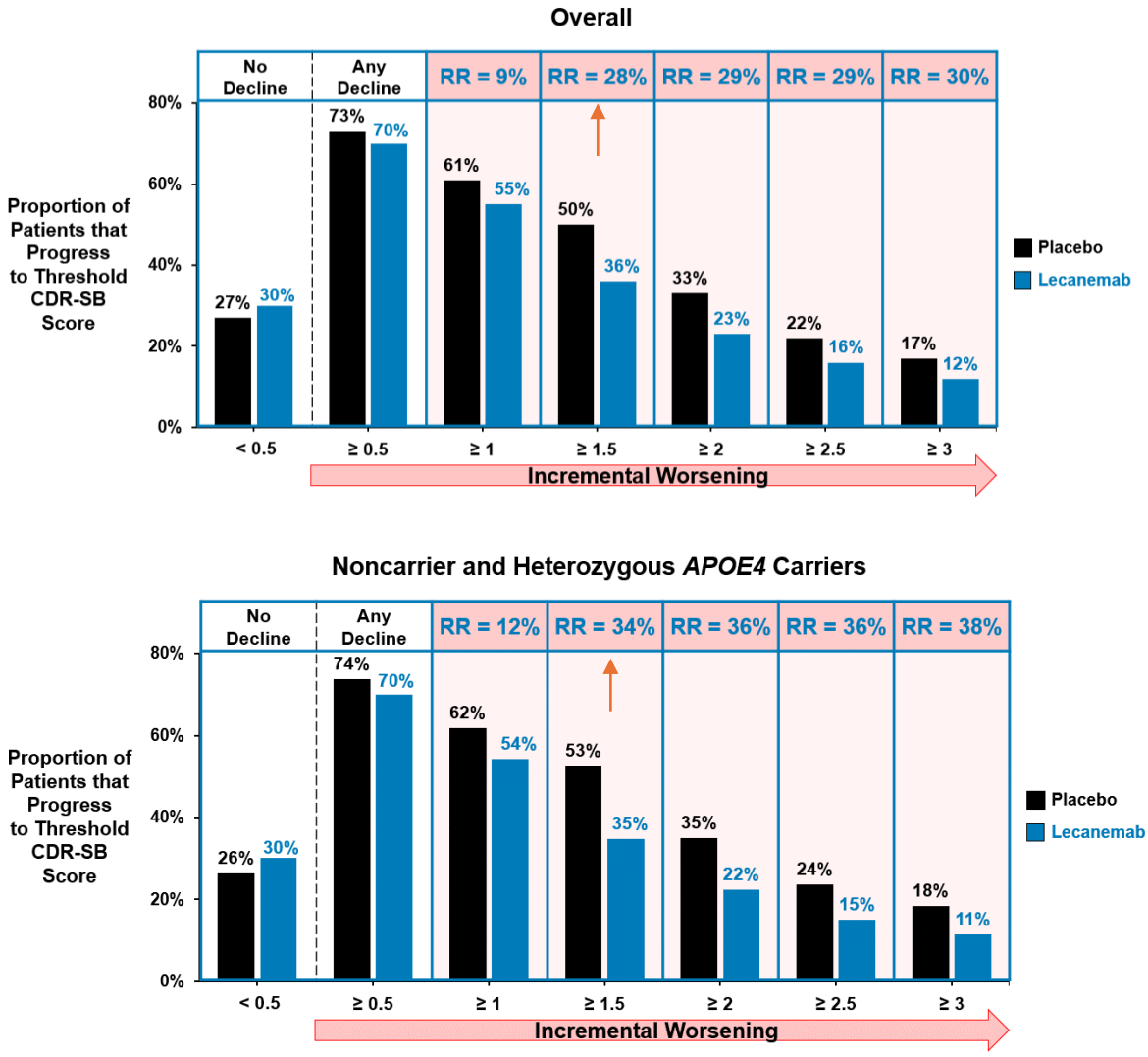


Figure 76. Progressor Analyses for the proportion of subjects with cognitive and functional worsening on CDR-SB – study 301 core (ITT)

APOE4 = apolipoprotein E4, CDR-SB = Clinical Dementia Rating-Sum of Boxes, ITT = intent to treat.

Delay in progression (or "**time-saved**" analyses according to the applicant's terminology) represents the difference in time until a specific decline in CDR-SB (e.g. 1.16) is expected under treatment and the time until the same specific decline in CDR-SB is expected under PBO (or natural history). It is, however, not the expected difference in time until this decline under treatment vs PBO. [i.e. the time until an outcome is expected is not the expected time until an outcome]. Expected time difference ("mean survival time") cannot be estimated due to censoring. Instead, restricted mean survival times may have been informative but were not provided. Restriction to 18 months would allow for a reliable estimation but, obviously, the restriction to 18 months would lead to only small effects underestimating the overall long-term effect.

The interpretation that the delay in progression (or "time saved" according to the applicant) analyses represent the time a patient remains with preserved cognition and function on treatment relative to PBO

or the natural history of AD holds only when the specific declines used for calculation of times saved are strict thresholds that separate patients with preserved cognition/function from those who lost it.

The analysis requires the assumption of a linear decline. The plausibility of this assumption is unclear. No goodness of fit is provided. The projections after 18 months require extrapolation, i.e. assuming that the decline continues with the same slope as observed until month 18. It cannot be verified whether this assumption is fulfilled (at least for placebo where no data after 18 months are available).

The results for CDR-SB are based on a prespecified slope analysis.

In the Overall Population, there is increasing separation over time between PBO and LEC10-BW, with a 29.3% slowing of progression on LEC10-BW annually ([95% CI: 16.1% to 42.4%], P=0.00001) versus PBO (see following figure). The PBO group reached the 18-month level of decline of the LEC10-BW group 5.3 months earlier. When projecting forward, LEC10-BW takes an additional 7.5 months to reach the clinical decline seen on PBO at 18 months (mean change in CDR-SB of 1.66).

In the Noncarrier and Heterozygous APOE4 Carrier Population, there is increasing separation over time between PBO and LEC10-BW, with a 34.0% slowing of progression on LEC10 BW annually ([95% CI: 20.2% to 47.8%]) versus PBO (see following figure). This separation indicates that cognition and function as assessed by CDR-SB is preserved by approximately 6.1 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW could take an additional 9.3 months to reach the clinical decline seen on PBO at 18 months (mean change in CDR-SB of 1.73). However, any assumption beyond 18 months is based on extrapolation of data and, as mentioned above, this may be too optimistic.

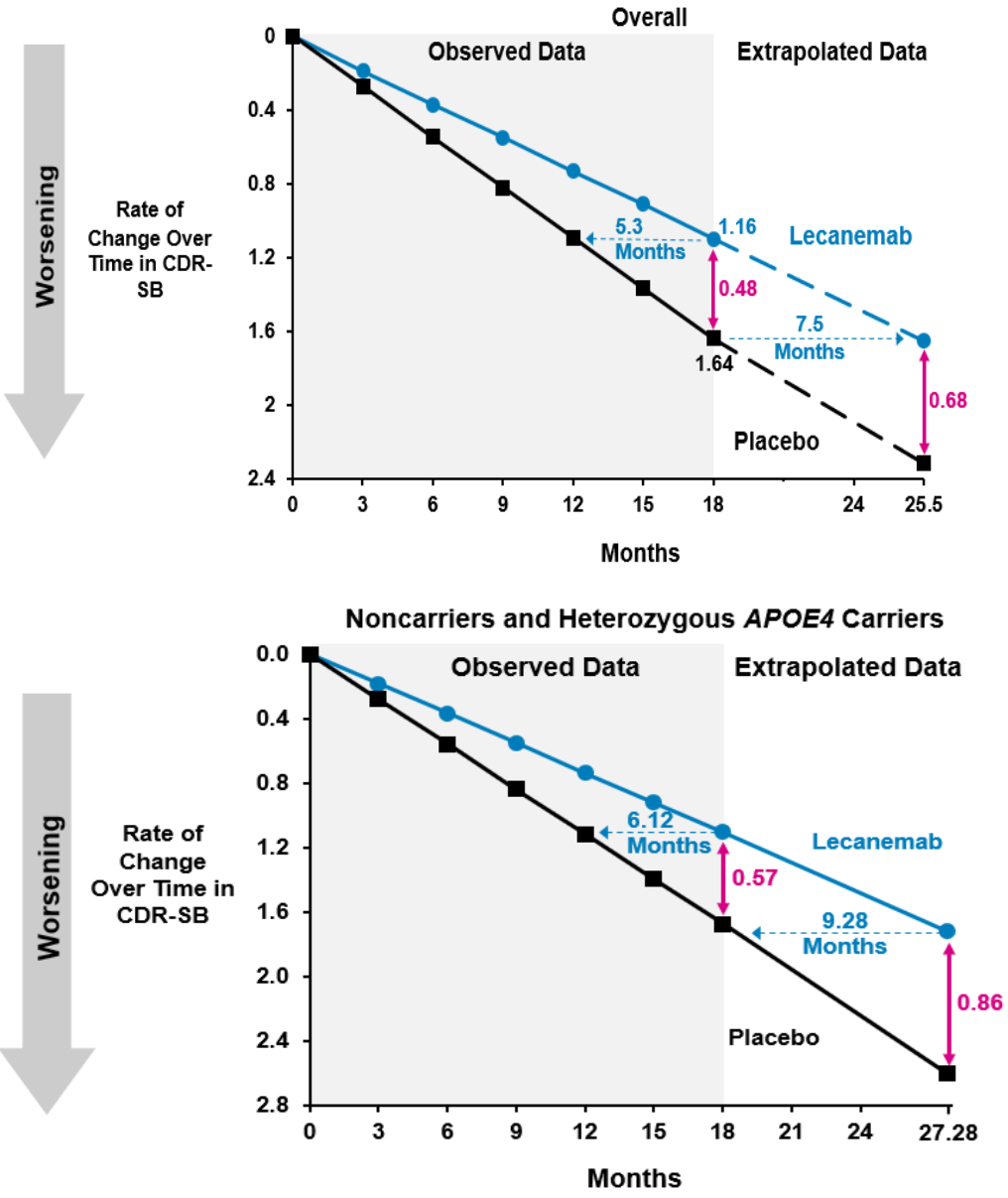


Figure 77. Analysis of rate of change over time of CDR-SB – study 301 core (mITT)

Change from baseline was analysed using LME model; LME model included time, and treatment by time as covariate with random intercept and slope.
APOE4 = apolipoprotein E4 variant, CDR-SB = Clinical Dementia Rating – Sum of Boxes, LME = linear mixed effects, mITT = modified intent to treat.

The same delay in progression (or "time saved" according to the applicant) analyses performed for the key secondary endpoints supported the outcome of the analyses with the CDR-SB and the results are very similar as compared to the overall population.

ADAS-Cog14

In the Overall Population, there is increasing separation over time between PBO and LEC10-BW. For ADAS-Cog14 there was 32.7% slowing of progression on `LEC10-BW annually ([95% CI: 16.7% to 48.7%], P=0.00006) versus PBO. This separation indicates that cognition as assessed by ADAS-Cog14 is preserved by approximately 5.9 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 8.8 months to reach the clinical decline seen on PBO at 18 months (mean change in ADAS-Cog14 of 5.58).

In the Noncarrier and Heterozygous APOE4 Carrier Population, there is increasing separation over time between PBO and LEC10-BW (see following figure). For ADAS-Cog14 there was 35.4% slowing of progression on LEC10-BW annually ([95% CI: 18.2% to 52.5%], P=0.00005) versus PBO. This separation indicates that cognition as assessed by ADAS-Cog14 is preserved by approximately 6.4 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 9.9 months to reach the clinical decline seen on PBO at 18 months (mean change in ADAS-Cog14 of 5.85).

It should be noted that estimates beyond 18 months are based on extrapolations and are not considered verifiable. Furthermore, information on ADAS-COG from the ADNI-cohort as control is not available.

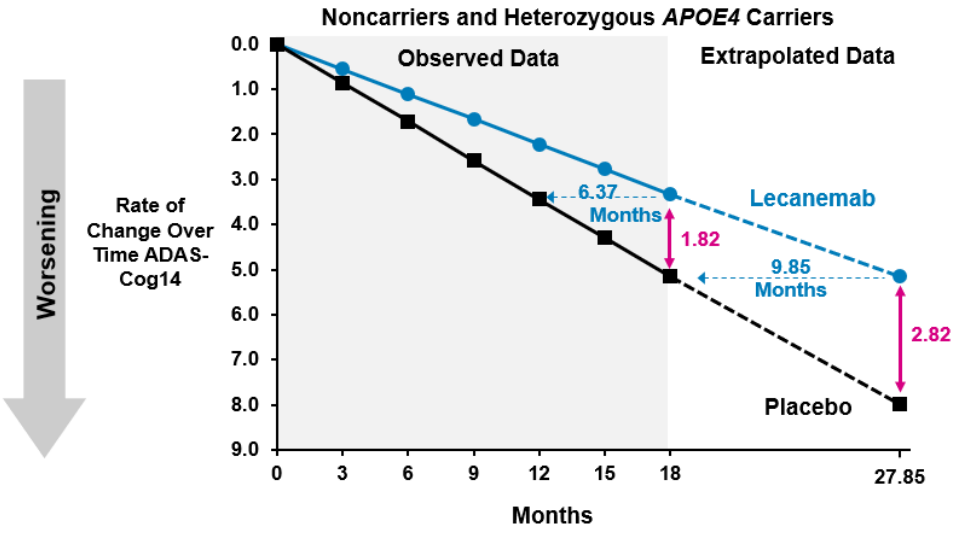


Figure 78. Analysis of rate of change over time of ADAS-Cog14 – study 301 core (mITT)

Change from baseline was analysed using LME model; LME model included time, and treatment by time as covariate with random intercept and slope.
APOE4 = apolipoprotein E4 variant, ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 item version, LME = linear mixed effects, mITT = modified intent to treat.

ADCS-MCI-ADL

In the Overall Population, there is increasing separation over time between PBO and LEC10-BW. For ADCS-MCI-ADL, there was 41.5% slowing of progression on LEC10-BW annually ([95% CI: 25.0% to 58.0%], P<0.00001) versus PBO. This separation indicates that function as assessed by ADCS-MCI-ADL is preserved by approximately 7.5 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 12.8 months to reach the clinical decline seen on PBO at 18 months (mean change in ADCS-MCI-ADL of -5.5).

In the Noncarrier and Heterozygous APOE4 Carrier Population, there is increasing separation over time between PBO and LEC10-BW. For ADCS-MCI-ADL, there was 44.2% slowing of progression on LEC10-BW annually ([95% CI: 26.6% to 61.9%], P<0.00001) versus PBO (see following figure). This separation indicates that function as assessed by ADCS-MCI-ADL is preserved by approximately 8 months on LEC10-BW relative to PBO during the 18-month Core. When projecting forward, LEC10-BW takes an additional 14.3 months to reach the clinical decline seen on PBO at 18 months (mean change in ADCS-MCI-ADL of -5.70). However, any assumption beyond 18 months is based on extrapolation of data and may be too optimistic.

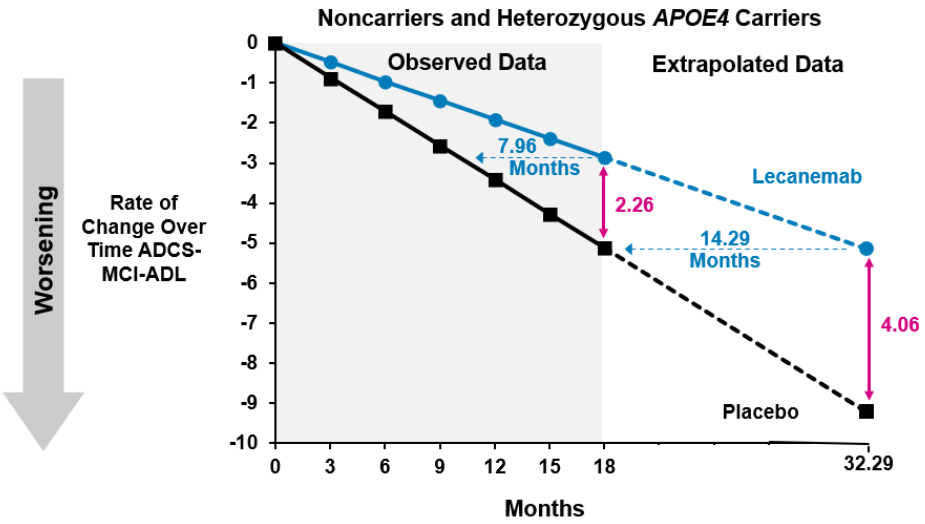


Figure 79. Analysis of rate of change over time of ADCS-MCI-ADL – study 301 core (mITT)

Change from baseline was analysed using LME model; LME model included time, and treatment by time as covariate with random intercept and slope.
APOE4 = apolipoprotein E4 variant, ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, LME = linear mixed effects, mITT = modified intent to treat.

Long-Term Progression

It is acknowledged that the median number of patients who worsened to the next stage in the treatment arms (LEC10-BW or PBO) was not reached within the controlled data time period of 18 months. This is expected due to the slow progression of patients and can explain why additional analyses from those that the applicant already conducted cannot be performed.

The applicant has therefore constructed a model for an analysis on time-to-worsening to the next disease stage for CDR-SB using actual 36-month data for LEC10-BW and the ADNI natural history cohort, and also incorporating 18-month PBO data from Study 301 Core to project delay in progression (or "time saved" according to the applicant) over 5 years after start of treatment (i.e., preserved cognition and function relative to PBO). The estimation from this model is quite optimistic and relies on unverifiable assumptions.

For this analysis, CDR-SB was chosen rather than global CDR for disease staging. Weibull distribution was used to model the time to worsening to next disease stage adjusting for important covariates like baseline disease stage and *APOE4* carrier status. Weibull distribution follows proportional hazard assumption same as the time to worsening analysis using Cox regression approach.

As was shown by the analyses on time to worsening of global CDR score, neither treatment arm reached the median number of events by 18 months.

Based on this model, ADNI cohort and PBO arm follow the same trajectory, confirming what is anticipated for the natural course of the disease and the observed placebo findings. It is also projected that ADNI natural history cohort/PBO arms reach the median number of events around 29 months (29.7 for PBO and 29.2 for ADNI) whereas the LEC10-BW arm reaches median number of events at 41 months, 12 months later (see following figure).

Additionally, it is projected that 66% of ADNI natural history cohort/PBO subjects would convert to next stage of disease by 42 months, whereas it will take 60 months for 66% of LEC10-BW to convert (see following table).

There may be limitations with the model and the assumptions used. However, the findings are again consistent with other analyses showing less decline in a given time period and a delay in disease progression measured by CDR-SB, ADAS-Cog14 and ADCS-MCI-ADL as well as delay in the progression of the disease (or "time saved" on disease progression, according to the applicant) with LEC10-BW treatment.

It is agreed with the applicant that these changes represent noticeable and relevant changes to patients and their ability to think and function.

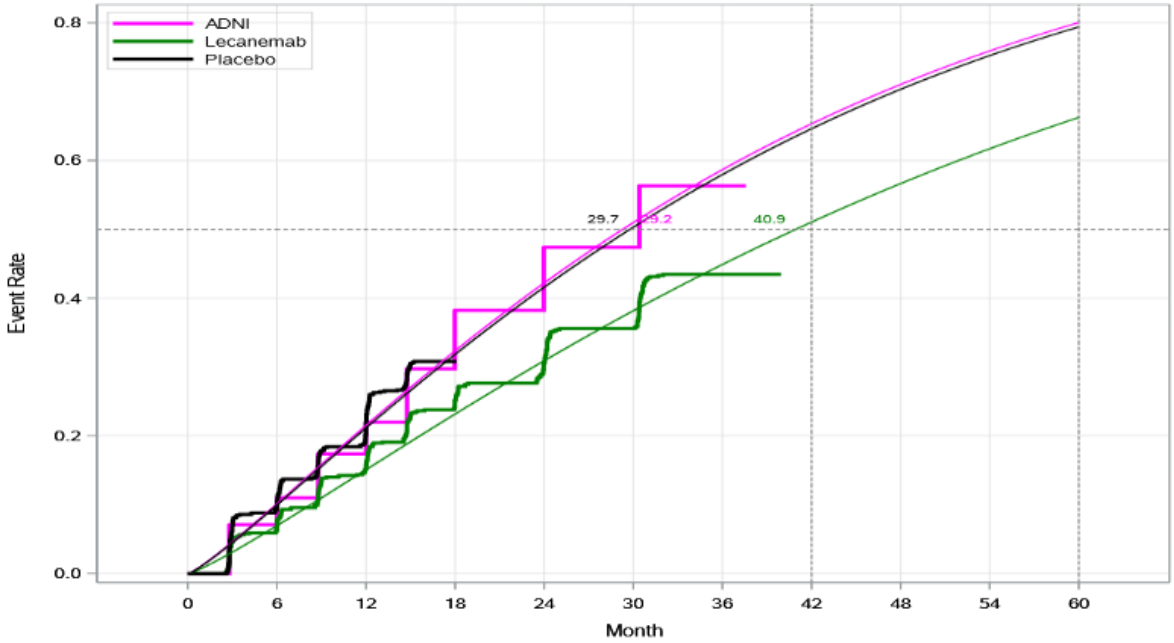


Figure 80. Event rate of time to worsening to next stage under Weibull distribution

Source: Data on file.

Table 104. Proportion of patients converting to the next stage of disease

Month	Lecanemab 10 mg/kg Biweekly	Placebo	ADNI
42	51.1%	**65.4%**	**64.7%**
60	**66.3%**	80.1%	79.4%

Source: Data on file.

Utilising the data from the core Study 301, the open label extension and the natural course of the disease (ADNI cohort), a Weibull model was fitted based on 36-month data for LEC10-BW and the ADNI natural history cohort, and also incorporating 18-month PBO data from Study 301. The validity of the model to make predictions beyond 36 months is unclear and not verifiable. Therefore, the projected 5 years outcome data are interesting but not appropriate for making robust conclusions on long-term benefit.

Sixty six percent of patients in the PBO or ADNI groups required 42 months to progress to the next stage of the disease, whilst the same percentage of patients (66%) in the LEC10-BW required 18 months more (60 months). This is a clear indication of benefits for Alzheimer's disease patients who remain at the same level of the disease for an 18-months longer period.

Changes in Health-Related Quality of Life Measures at 18 Months

Maintaining health-related quality of life in Alzheimer's Disease has been identified as a clinically meaningful benefit by both the patient and care partner, with health-related quality of life assessments providing unique perspectives from the patient and care partner with respect to their own perceptions of how the disease affects them (Lawton, 1994, Barbe, et al., 2018). The progression of disease is distressing for patients, their care partners, and their families.

In Study 301, at 18 months, the adjusted mean change from baseline in European Quality of Life-5 Dimensions 5 Level version (EQ-5D-5L) and Quality of Life in Alzheimer's disease (QOL-AD) rated by the patient showed 49% and 56% less decline compared to placebo, respectively. Study partner burden as measured by adjusted mean change from baseline at 18 months using the Zarit Burden Interview resulted in 38% reduction in care partner burden. For each health-related quality of life subject assessment, results are in favour of LEC10-BW beginning from the time-point of 6 months.

Tangible benefits for patients and their care partners were obtained as measured by health-related quality of life outcomes. Unlike for PBO subjects, those treated with LEC10-BW had less decline in mood, self-care, finances and life as a whole.

Additional Subgroup Analyses at 18 Months

The following new information provided by the applicant addresses a potential increase benefit with earlier treatment initiation. Since it has already been published at AAIC 2024 (van Dyck, 2024) it is shortly mentioned. However, treatment in earlier stages of AD will be addressed in the ongoing study 303 and the Tau data do not solve this uncertainty.

The tau PET substudy of Study 301 included 342 patients with baseline tau PET scans, whose baseline characteristics were representative of the overall study population. The Applicant performed analyses stratified tau PET by no/low tau (consistent with early-stage), intermediate tau (consistent with intermediate-stage), and high tau (consistent with advanced stage) based on standardised uptake value ratio (SUVr).

Data from the no/low tau population in Study 301 Core (PBO N=67, LEC10-BW N=63) indicate that early initiation of therapy not only slows progression but also can stabilise or even improve clinical outcomes:

- More subjects demonstrated no decline with LEC10-BW treatment than PBO on CDR-SB at 18 months (PBO: 32/58, 55%; LEC10-BW: 38/50, 76%) at 18 months.
- More subjects demonstrated an improvement with LEC10-BW treatment than PBO on CDR-SB (PBO: 16/58, 28%, LEC10-BW: 30/50, 60%) at 18 months.

For no/low tau subjects the results seen at 18 months were sustained though 36 months.

Similar results were seen for ADAS-Cog14 and ADCS-MCI-ADL.

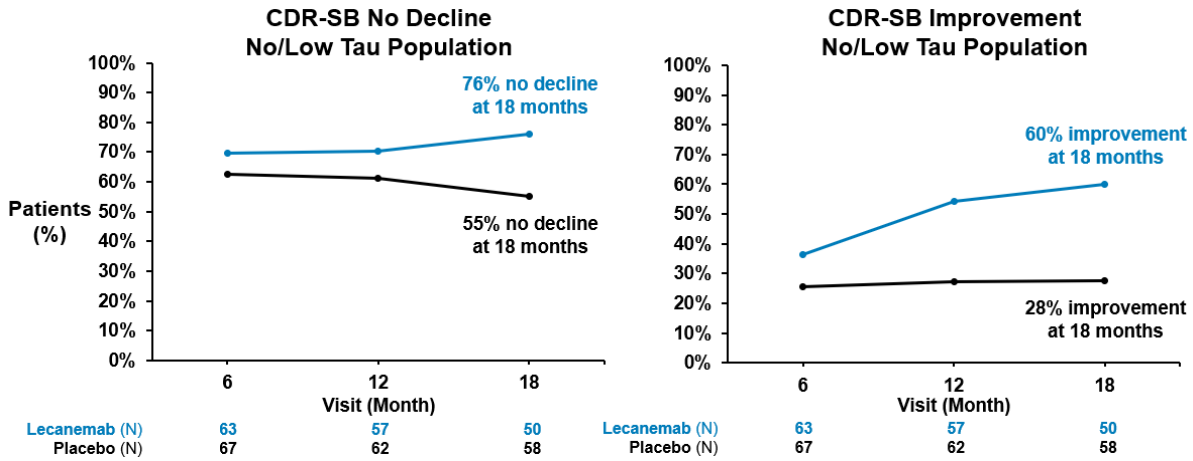


Figure 81. CDR-SB at 18 months in no/low Tau PET subjects – study 301 core (Tau PET substudy)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, PET = positron emission tomography.

The results seen at 18 months for the no/low tau subgroup were sustained through 36 months:

- At 36 months, 24/41, 59% of subjects demonstrated no decline on CDR-SB with LEC10-BW.
- At 36 months 21/41, 51% of subjects continued to show improvement on CDR-SB with LEC10-BW.

Data from the low amyloid population (<60 CL population in Study 301 Core (PBO N=176, LEC10-BW N=178) also indicate that early initiation of therapy not only slows progression but also can stabilise or improve clinical outcomes:

- More subjects demonstrated no decline with LEC10-BW treatment than PBO on CDR-SB (PBO: 75/161, 46.6%; LEC10-BW: 85/146, 58.2%) at 18 months.
- More subjects demonstrated an improvement with LEC10-BW treatment than PBO on CDR-SB (PBO: 41/161, 25.5%, LEC10-BW: 54/146, 37.0%) at 18 months.

The results seen at 18 months were sustained though 36 months.

Similar results were seen for ADAS-Cog14 and ADCS-MCI-ADL.

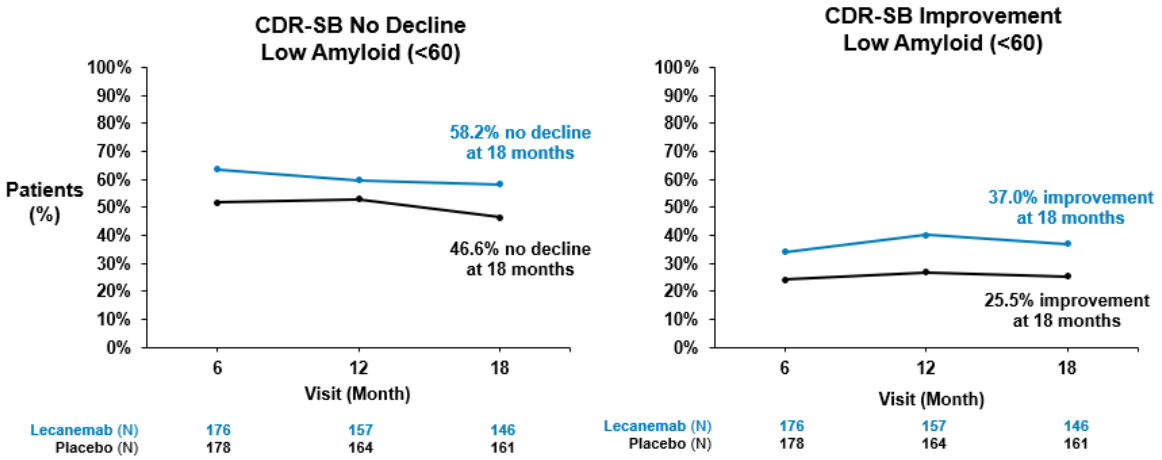


Figure 82. CDR-SB at 18 months in low amyloid PET subjects – study 301 core (amyloid PET substudy)

CDR-SB = Clinical Dementia Rating-Sum of Boxes, PET = positron emission tomography.

The results seen at 18 months for the low amyloid PET subgroup (Section 0) were sustained through 36 months:

- At 36 months, 53/115, 46.1% of subjects demonstrated no decline with LEC10-BW.
- At 36 months 38/115, 33.0% of subjects continued to show improvement on CDR-SB.

It should be pointed out that the applicant has already initiated a study in pre-symptomatic patients. Study 303 (AHEAD - NCT04468659), which will assess lecanemab in individuals with preclinical Alzheimer disease (AD) who have no cognitive symptoms present.

Overall conclusion on the applicant's grounds for re-examination:

Small but statistically significant effects on both the primary and key secondary endpoints have already been demonstrated for the overall population at 18 months. Additional analyses for the Noncarrier and Heterozygous APOE4 Carrier Population included

- change from baseline for CDR-SB at 18 months compared to placebo and 36 months compared to an ADNI natural history cohort,
- change from baseline for ADAS-Cog14 and ADCS-MCI-ADL at 18 and 36 months (with the 18-month data being placebo controlled),
- time to worsening of global CDR,
- time to event analyses,
- progressor and delay in progression (or time-saved according to the applicant) analyses.

A 5-year projection model was also constructed based on all available data form Study 301 and ADNI.

These post-hoc analyses in the Noncarrier and Heterozygous APOE4 Carrier Population are consistent with the results in the overall population and further support that lecanemab LEC10-BW treatment achieved:

- ✓ slowing of disease progression measured by CDR-SB, ADAS-Cog14 and ADCS-MCI-ADL at 18 months as well as
- ✓ less decline in a given time period (18 and 36 months) compared to placebo or to a natural history cohort
- ✓ reduced the risk of worsening by 0.5 or by 2.0 on CDR-SB (by 22% and 37% respectively)

- ✓ reduction in the relative risk of patients progressing with 1.5-point decline on CDR-SB (by 34%) compared to placebo

The model-based time-saved analyses suggest that the placebo group reached the 18-month level of decline in CDR-SB of the LEC10-BW group 6.1 months earlier. The separation in clinical measures from untreated patients seems to increase over time, which is supported by comparison to the ADNI natural history cohort over 36 months and a modelling exercise over 5 years. However, long-term projections, especially over 5 years rely on assumptions that are not really verifiable. These results in the Overall population and in the noncarrier and heterozygous subpopulation translate into quality of life and activities of daily living benefits for both patients and carers.

The additional efficacy analyses provide reassurance of a positive benefit/risk balance.

Overall, it can be concluded that the safety of lecanemab (Leqembi) has been sufficiently demonstrated based on

- the data from the phase 3 study and supportive phase 2 and OLE data,
- a restricted patient population (noncarriers and heterozygous carriers for APOE4), and
- the proposed extensive risk minimisation measures.

By exclusion of the homozygous APOE4 population from treatment with lecanemab ARIA and ICH > 1 cm are manageable by the proposed risk minimisation measures in the now indicated population.

5.3. Risk Management Plan

5.3.1. Safety concerns

Important identified risks	• ARIA-E/vasogenic cerebral oedema • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • ARIA intracerebral haemorrhage >1 cm in diameter
Important potential risks	• Acceleration of disease progression due to ARIA induced brain atrophy
Missing information	None

ARIA-E = amyloid-related imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities - microhaemorrhage and hemosiderin deposit.

5.3.2. Pharmacovigilance plan

Study name and description **Study status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
<u>Category 1</u> – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Registry Pending. *Will be amended, when the protocol is approved*.	• Further characterise ARIA-E, -H and ICH>1 cm and assess possible acceleration of disease progression due to ARIA (progression to the next stage of AD), effectiveness of risk minimisation measures and drug utilisation • To evaluate compliance and effectiveness of the risk minimisation measures described in SmPC and the HCP educational material.	ARIA-E, ARIA-H and ICH >1cm Acceleration of disease progression due to ARIA induced brain atrophy	Draft protocol	January 2025
			Final protocol	March2025
			Progress reports	Annually starting 2026
			Final report	To be determined
<u>Category 2</u> – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	N/A	N/A	N/A	N/A
<u>Category 3</u> – Required additional pharmacovigilance activities				
BAN2401-G000-301 OLE	Evaluate the long-term safety and tolerability of LEC10-BW in subjects with early Alzheimer's disease in the Extension Phase.	Acceleration of disease progression due to ARIA induced brain atrophy	Interim Report	Mar 2026
			Final report submission	2030
BAN2401-G000-303	To evaluate efficacy and safety of lecanemab in the preclinical AD population.		Interim Report	Not applicable
			Final report submission	Feb 2030

5.3.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
ARIA--E/vasogenic cerebral oedema	Routine risk communication: • SmPC Section 4.8 and PL Section 4 where ARIA-E is listed as an ADR • SmPC Sections 4.3, 4.4 and 4.8 where relevant clinical information from clinical studies on the incidence, nature, and risk factors of ARIA-E is provided • PL Additional risk minimisation measures: • Patient Card • Guide for healthcare professionals • Controlled Access Programme	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • Registry (Cat 1 study) will characterise the risks of ARIA-E, ARIA-H and ARIA ICH > 1cm
ARIA-H (Cerebral Microhaemorrhage and Superficial Siderosis)	Routine risk communication: • SmPC Section 4.8 and PL Section 4 where ARIA-H is listed as an ADR • SmPC Sections 4.3, 4.4 and 4.8 where relevant clinical information from clinical studies on the incidence, nature, and risk factors of ARIA-H is provided • PL Additional risk minimisation measures: • Patient Card • Guide for healthcare professionals • Controlled Access Programme	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • Registry (Cat 1 study) will characterise the risks of ARIA-E, ARIA-H and ARIA ICH > 1cm
ARIA Intracerebral Haemorrhage >1 cm in diameter	Routine risk communication: • SmPC Section 4.3, 4.4 and PL Section 4 where ARIA intracerebral haemorrhage >1 cm is listed as an AE that has occurred in patients treated with lecanemab and also occurring spontaneously in patients with AD. • SmPC Sections 4.4 and 4.8 where relevant clinical information from clinical	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • AE follow-up form for adverse reaction Additional pharmacovigilance activities: • Registry (Cat 1 study)will characterise the risks of ARIA-E, ARIA-H and ARIA ICH > 1cm

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	studies on the incidence, nature, and risk factors of ARIA is provided • PL Additional risk minimisation measures: • Patient Card • Guide for healthcare professionals • Controlled Access Programme	
Important Potential Risk		
Acceleration of disease progression due to ARIA induced brain atrophy	Routine risk minimisation measures • N/A Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Data from ongoing studies BAN2401-G000-301 OLE and BAN2401-G000-303 will be used to further characterise the important potential risks of "Acceleration of disease progression due to ARIA induced brain atrophy". • Registry (Cat 1 study) will characterise the risks of ARIA-E, ARIA-H and ARIA ICH > 1cm
Missing Information		
None		

ADR = adverse drug reaction, AE = adverse event, ARIAE = amyloid related- imaging abnormalities – oedema/effusion, ARIA-H = amyloid-related imaging abnormalities microhaemorrhage- and hemosiderin deposit, PL = Package Leaflet, SmPC = Summary of Product Characteristics.

5.3.4. Conclusion

The CHMP considers that the risk management plan version 0.92 is acceptable.

5.4. Pharmacovigilance

5.4.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.4.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06.01.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

Alzheimer's disease is a progressive neurodegenerative disorder characterised by cognitive and functional decline, and the main cause of dementia. AD is ultimately fatal.

According to the World Alzheimer Report 2018 more than 50 million people worldwide are living with dementia, and in the European population the prevalence of AD is estimated at 5.05 million (Niu, 2017). According to a review in US, the prevalence of MCI is estimated around 8-10% for adults aged 60-69 years, 15% for adults aged 70-79%, and 25% for elderly aged 80-84 years (Perterson, 2018).

Lecanemab was developed as a treatment for AD. Lecanemab is a monoclonal antibody that binds with highest affinity to large soluble amyloid beta (Aβ) protein aggregates, known as protofibrils. The claimed indication was initially: a disease modifying treatment in adult patients with Mild Cognitive Impairment due to Alzheimer's disease and Mild Alzheimer's disease (Early Alzheimer's disease). It is to note that the presence of amyloid beta (Aβ) pathology must be confirmed via an appropriate test prior to initiating treatment. During the procedure, the applicant modified the indication targeted as follows: the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) in adult patients with confirmed amyloid pathology.

For the re-examination procedure, after CHMP feedback, the applicant proposed a restricted indication with a narrower patient population:

Lecanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (early Alzheimer's disease) in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or noncarriers with confirmed amyloid pathology.

6.1.1. Disease or condition

AD is an irreversible and progressive neurodegenerative disease that affects memory, thinking, and behaviour, and is ultimately fatal. Earlier intervention before decline accelerates can slow the increasingly rapid accumulation of even more consequential, irreversible, functional losses and therefore provide increasing long-term benefits for patients. The ApoE ε4 allele is the strongest known genetic risk factor for AD.

For patients, symptoms grow severe enough to interfere with daily tasks (feeding, dressing, bathing, continence) resulting poor health-related quality of life and a loss of independence. The gradual progression of disease is distressing for patients, their care partners, and their families. The increased dependency and emotional changes contribute significantly to care partner burden, putting them at increased risk for physical morbidity and mental disorders (Sörensen and Conwell, 2011).

Early AD (MCI due to AD and mild AD dementia) is the stage of AD where in general compromised memory and thinking first appear, and may present as problems with memory, language, or

judgement, as precursors to the beginning of functional decline associated with dementia. Early AD is often minimised and mistakenly attributed to normal aging. In the earliest symptomatic stage of AD (MCI due to AD), a patient's cognitive function is impaired (Jekel, et al., 2015), with difficulties in wordfinding, losing items, and forgetting appointments and other important recent events. This can result in feelings of anxiety, shame and fear for the future. Individuals with mild symptoms often may continue to work, drive and participate in their favourite activities, with occasional help from family members and friends (2024 Alzheimer´s disease facts and figures; DOI: 10.1002/alz.13809). However, the ability to function and health-related quality of life will decline relentlessly to the point of severe dependence and then premature death (Tifratene, et al., 2015; Boyle, et al., 2006). By the moderate AD stage, patients can no longer perform these instrumental daily activities, and basic activities become impaired.

In Europe, AD and other dementias were estimated to be the third leading cause of death for people 70 years and older, with approximately 640,000 deaths attributable to dementia in this age group in 2017 (Ritchie, 2019). Alzheimer Europe, an NGO representing patients with dementia, estimates that in 2018 as many as 7.8 million EU citizens, two-thirds of them women, were suffering from this disorder (European parliament 2022).

Risk factors for ARIA-E, H, and ICH>1 cm in natural history studies are cerebral amyloid angiopathy (CAA) (including evidence of prior microhaemorrhage and superficial siderosis) and an increasing number of APOE4 alleles. Three mechanisms by which APOE4 influences ARIA risk have been recently hypothesised: (1) reduced cerebrovascular integrity, (2) increased neuroinflammation and immune dysregulation, and (3) elevated levels of CAA. The effects of APOE4 on ARIA risk is clear, however, the underlying mechanisms require more research (Foley and Wilcock 2024).

6.1.2. Available therapies and unmet medical need

Currently, pharmacological treatment approved in Europe (i.e. cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine) are targeted toward symptomatic therapy only.

In Europe, there are no therapies approved that modify the course of the clinical disease progression at any stage of the disease.

Overall, there is a need for disease modifying therapies.

6.1.3. Main clinical studies

The main evidence of efficacy is based on a single Phase 3 study, BAN2401-G000-301 (Study 301), a global, multicentre, double-blind, placebo-controlled, parallel-group trial in subjects with EAD that evaluated LEC10-BW for 18 months to confirm the safety and efficacy of lecanemab. The core phase was followed by an open label phase (Open-label Extension (OLE)) evaluating a dose of LEC10-BW in all subjects.

6.2. Favourable effects

The analysis for the primary endpoint of the pivotal study, using a control-based imputation, showed for the overall population a statistically significant difference of -0.401 (95%CI -0.622, -0.180) between lecanemab and placebo in change from baseline in CDR-SB at 18 months.

Additionally, the 3 key clinical endpoints showed for the overall population statistically significant differences in favour of lecanemab versus placebo: -1.442 (95%CI: -2.270, -0.613; p=0.00065) in

change from baseline in ADAS-Cog14 at 18 months, -0.050 (95%CI: -0.074, -0.027; p=0.00002) in change from baseline in ADACOMS at 18 months, and 2.016 (95% CI; 1.208, 2.823; p<0.00001) in change from baseline in ADCS MCI-ADL at 18 months.

Regarding the pharmacodynamics, the first key secondary endpoint, change from baseline in amyloid PET using centiloids, showed a decrease in brain amyloid level over the study duration. In Study 301 Core, the adjusted mean treatment difference between LEC10-BW and PBO was statistically significant -59.1 (P<0.00001). The adjusted mean change from baseline in amyloid PET using centiloids at 18 months was increased for PBO (3.6) and substantially decreased for LEC10-BW (-55.5). The baseline level was 77.9 centiloids, and at the end of the study the level was 23.0 in the LEC10-BW group.

For the Re-examination, the applicant excluded the homozygous APOE4 population from the originally claimed indication and performed several efficacy analyses for the Noncarrier and heterozygous *APOE4* Carrier subpopulation.

CDR-SB

- At 18 months, the adjusted mean treatment difference in the change from baseline for CDR-SB for the Noncarrier and Heterozygous *APOE4* Carrier Population (using the same control-based imputation as for the overall population above) was -0.535 (95% CI:-0.778, -0.293) corresponding to 33.5% less decline with LEC10-BW compared to PBO. At 36 months the adjusted mean treatment difference was -0.86 between LEC10-BW and an external control (ADNI cohort) corresponding to a delay of 6.8 months in progression.

ADAS-Cog14

At 18 months, the adjusted mean treatment difference in the change from baseline for ADAS-Cog14 for the Noncarrier and Heterozygous *APOE4* Carrier Population was -1.512 (95% CI: -2.486, -0.538) corresponding to 27.9% less decline with LEC10-BW compared to PBO. At 36 months, a comparison to ADNI could not be performed because ADAS-Cog was not tested in ADNI. The comparison was performed between LEC10-BW early start and the delayed start and the adjusted mean treatment difference in the change from baseline at 36 months was **-1.56**, nominal *P*=0.05215

ADCS-MCI-ADL

At 18 months, the adjusted mean treatment difference in the change from baseline for ADCS-MCI-ADL for the Noncarrier and Heterozygous *APOE4* Carrier Population was 1.936 (95% CI: 1.029, 2.844) corresponding to 39.2% less decline with LEC10-BW compared to PBO. Due to the lack of ADNI data, at 36 months the comparison was performed between LEC10-BW early start and the delayed start and the adjusted mean treatment difference in the change from baseline was **1.80**, *P*=0.01236.

Progressor and time to event analyses

The presented estimations for the **time to event analyses** (with event defined as decline by 0.5 and 2.0 on CDR-SB) at 18 months for the Noncarrier and Heterozygous *APOE4* Carrier Population indicated that the HR of worsening was 0.782 (95% CI [0.687,0.892] for the 0.5 points decline) and 0.634 (95% CI [0.513, 0.784] for the 2 points decline.

In the **progressor analyses**, a 1.5-point decline on CDR-SB, representing the median decline for PBO, would generally reflect a subject deteriorating in more than one cognitive or functional CDR-SB domains. For the Noncarrier and Heterozygous APOE4 Carrier Population, at 18 months, 53% of PBO subjects declined compared to 35% of LEC10-BW subjects.

The **presented model-based "time-saved" analyses** estimate the difference in time until a specific decline in CDR-SB is expected under treatment and the time until the same specific decline in CDR-SB is expected under PBO (or natural history). This difference was estimated to be 6.1 months for the

Noncarrier and Heterozygous *APOE4* Carrier Population suggesting that the PBO group reached the 18-month level of decline of the LEC10-BW group **6.1 months earlier**.

Regarding the pharmacodynamics for the restricted population (APOE4 noncarriers and heterozygotes), change from baseline in amyloid PET using centiloids, showed a decrease in brain amyloid level, which was comparable with the overall population. At 18 months, the adjusted mean change from baseline in amyloid PET using centiloids was increased for PBO (3.895) and substantially decreased for LEC10-BW (-55.541). A statistically significant adjusted mean treatment difference between LEC10-BW and PBO of -59.437 (95% CI: -63.291, 55.582) at 18 months was observed.

6.3. Uncertainties and limitations about favourable effects

The confirmatory evidence comes from a single pivotal trial. However, in line with the Points to consider on application with 1. meta-analyses; 2. one pivotal study, in this case there is no strict requirement for replication since there is a strong pharmacological rationale and biological plausibility for the mechanism of action of lecanemab as confirmed by the biomarker findings, and overall supportive phase II data, especially the data regarding the gap of the treatment.

Furthermore, there are no indications of a potential bias, the selected population has been restricted and internal consistency exists, and the statistical significance is considerably stronger than $p<0.05$ (CPMP/EWP/2330/99).

The size of the effect in the primary analysis (-0.451 in change from baseline in CDR-SB at 18 months) for the overall population is considered small. It should be noted that the primary analysis based on a MMRM model rather targets a hypothetical estimand with respect to the intercurrent event "treatment discontinuation" and is expected to overestimate the treatment policy estimand. In order to target the more relevant treatment policy estimand, the results of the control-based multiple imputation for missing data handling are more relevant for assessment. The applicant provided such an analysis, which led to a lower estimate of the effect (-0.401).

Currently there is a lot of discussion in the field and literature about the clinically relevant treatment effect size in early Alzheimer's disease.

There are uncertainties on the long-term efficacy, since the placebo-controlled data are limited to 18 months with further data from the OLE period up to 36 months. A formal statistical comparison between LEC10-BW and the Alzheimer's Disease Neuroimaging Initiative (ADNI) natural history cohort at 36 months could not be performed. However, the trajectories of the PBO in study 301 Core and ADNI natural history cohort for the first 18-month period were almost overlapping. The presented information beyond 18 months are based on extrapolation using unverifiable models and assumptions. Moreover, ADAS-COG and ADCS-MCI-ADL are not available for the ADNI cohort. Missing data in the ADNI cohort is considerable (60% in the restricted population). Thus, treatment effect estimates at 36 months may be biased.

Whereas the presented delay in progression or "time-saved" analyses estimate the difference in time between active and placebo treatment until a specific decline is expected under treatment. It is, however, not the expected difference in time until this decline under treatment vs PBO [i.e., the time until an outcome is expected is not the expected time until an outcome]. Expected time difference ("mean survival time") cannot be estimated due to censoring. Instead, restricted mean survival times may have been informative but were not provided. Restriction to 18 months would allow for a reliable estimation but, obviously, the restriction to 18 months would lead to only small effects. The provided analyses make the assumption of a linear decline. The plausibility of this assumption remains unclear. However, it should be taken into consideration that although the natural course of disease may be

approximated with a linear model over time, it is yet unclear whether a linearity assumption holds true in the situation of a clinical trial with an intervening (potentially disease-modifying) treatment effect and whether the effect of treatment is constant over the treatment course (CPMP/EWP/553/95 Rev.2, Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease).

Projections after 18 months require extrapolation, i.e., assuming that the decline continues with the same slope as observed until month 18. It cannot be verified whether this assumption is fulfilled (at least for placebo where no data after 18 months are available)

There is insufficient information with respect to the duration of treatment and stopping. The results from study 201 before, during and after the treatment gap show that patients who stopped treatment in the gap period deteriorated on biomarkers and clinically. However, it remains still unclear how long patients should be treated. The following phrase is included in the SmPC: "*Treatment with lecanemab should be discontinued once the patient progresses to moderate Alzheimer's disease*".

There were inconclusive findings on the favourable effect in the APOE4 homozygous carriers, while this population is particularly at risk for AD and ARIA events. In the case of homozygous APOE4 carriers, some results were numerically in favour of LEC10-BW e.g. the treatment difference between LEC10-BW and PBO in the change from baseline at 18 months for ADAS-Cog14 and ADCS-MCI-ADL, whilst the findings on CDR-SB were not. The results for this subgroup are in contrast with the expectation that a higher benefit was expected in ApoE ε4-carriers because of the mechanism of action. Recent literature suggests that APOE-e4 homozygous might represent another form of genetically determined AD (Fortea et al., 2024; Xu et al., 2024).

6.4. Unfavourable effects

The grounds for refusal of lecanemab are based on the occurrence of amyloid-related imaging abnormalities (ARIA) in the phase 3 study and the clinical consequences deriving thereof, i.e. symptomatic ARIA and ICH>1cm. The incidence and severity of ARIA-E and -H increased with the number of *APOE4* alleles. The applicant provided a post-hoc analysis for ARIA as the key unfavourable effect separated by APOE4 carrier status (homozygous, heterozygous, and noncarriers of APOE4). The incidences of symptomatic ARIA-E and ARIA-H were noticeable in APOE4 homozygous carriers (9.2% and 3.5%, respectively), as were the ARIA - related TEAEs leading to withdrawal (10.6%).

ARIA-E occurred with the frequency "very common" for heterozygous carriers of APOE4 and with common frequency in noncarriers. ARIA-H occurred with very common frequency for all APOE4 genotypes. ARIA-E and ARIA-H occurred isolated or concurrent with each other.

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

In the LEC10-BW group, homozygous APOE4 carriers had a higher incidence of **ARIA-E** (32.6%; 3.8% for placebo). When homozygous APOE4 carriers are removed from the analyses (noncarrier and heterozygous APOE4 carriers only), the incidence was 8.9% (vs. 1.3% for placebo). The incidence of ARIA-E in the OLE of study 301 was consistent with the core period.

65% of all ARIA-E events were concurrent with ARIA-H in the overall LEC10-BW group versus 54% of all ARIA-E events in the noncarrier and heterozygous APOE4 population.

Most cases of ARIA-E occurred within the first 6 months, and did not increase with longer treatment of up 36 months in the OLE, irrespective of APOE4 genotype; most events resolved after 4 months.

Radiographic severity of ARIA-E events was mainly mild or moderate and rated severe in 3% of APOE4 noncarriers and heterozygous APOE4 carriers during the 18 months treatment period in 301 core.

In APOE4 noncarriers and heterozygous APOE4 carriers, **serious ARIA-E** and **symptomatic ARIA-E** events occurred with an incidence of 0.5% (0% for placebo) and 1.6% (0% for placebo) in the 301 core study, and both did not increase in the OLE of study 301.

Based on the totality of ARIA-E events in the intended population (N=67), N=4 were serious (6%), and N=12 were symptomatic (18%).

The most common symptoms with ARIA-E were headache, confusional state, dizziness, and nausea. The majority of symptomatic ARIA-E were mild or moderate (for all genotypes). Severe symptomatic ARIA-E in the intended patient population in 301 core occurred in 2 patients, both heterozygous APOE4 carriers, and involved aphasia and generalised tonic-clonic seizure.

Most subjects of the intended population experienced only one ARIA-E event, while 8 of 67 patients (12%) with ARIA-E experienced a recurrent event. Additional occurrences were rare with one patient experiencing 4 events of ARIA-E. Recurrence of ARIA-E is addressed in the SmPC sections 4.2, 4.4, and 4.8.

Based on the overall data on ARIA-E, SmPC section 4.2 recommends continuing lecanemab if ARIA-E is asymptomatic and radiographically mild. Lecanemab should be interrupted if symptomatic or radiographically moderate or severe ARIA-E occurs; a follow-up MRI 2 to 4 months after initial identification should be conducted to confirm radiographic resolution or absence of symptoms. Lecanemab should be discontinued after the second occurrence of symptomatic or asymptomatic moderate or severe ARIA-E.

ARIA-H (with or without concurrent ARIA-E) was observed in 13% (98/757) of the intended patient population treated with lecanemab, of which 80% (78/98) continued on lecanemab treatment with or without dose interruption. Among those that continued lecanemab, 36% (28/78) experienced a recurrence of ARIA-H.

In the LEC10-BW group, homozygous APOE4 carriers had a higher incidence of **ARIA-H** (38.3%; 21.1% for placebo). When homozygous APOE4 carriers are removed from the analyses (noncarrier and heterozygous APOE4 carriers), the incidence was 12.9% (vs. 6.8% for placebo). The incidence of ARIA-H in the OLE of study 301 was slightly higher as in the core period (19.3%). The incidence of isolated ARIA-H (in the absence of ARIA-E) with LEC10-BW in the intended population was similar (8.1% for LEC10-BW and 5.9% for placebo).

In 62% of noncarriers and APOE4 heterozygous carriers with ARIA-H, the ARIA-H was isolated, while for 38% of noncarriers and APOE4 heterozygous carriers, the ARIA-H was concurrent with ARIA-E. ARIA-H concurrent with ARIA-E (like ARIA-E alone) generally occurs early in treatment with the majority of events (~90%) within the first 6 months; however, isolated ARIA-H has been observed throughout the treatment period.

Radiographic severity of overall (and isolated) ARIA-H events was mainly mild or moderate and rated as severe (severe ARIA-H microhaemorrhage is defined as ≥ 10 new incident microhaemorrhages and ARIA-H superficial siderosis > 2 areas of superficial siderosis) in 1.6% (0.3%) and driven by ARIA-H microhaemorrhages. Severity only slightly worsened over the 36 months period (2.5% of overall ARIA-H and 0.6% of isolated ARIA-H was rated as severe).

Cerebral microhaemorrhage had the highest incidence among PTs of ARIA-H and its difference was highest between the treatment arms with 14% in the overall LEC10 BW group and 7.6 % in the placebo group. Microhaemorrhage ≤ 10 was more frequent than microhaemorrhage >10 for noncarriers and heterozygous carriers of APOE4 treated with lecanemab (10.2% and 1.1%).

In APOE4 noncarriers and heterozygous APOE4 carriers, **serious ARIA-H** and **symptomatic ARIA-H** events occurred with an incidence of 0.1% (0% for placebo) and 0.8% (0.1% for placebo) in the 301 core study. Based on the 301 core and OLE experience, serious AEs of ARIA-H were all concurrent with ARIA-E events and none resolved. Based on the totality of ARIA-H events in the intended population (N=98), N=1 was serious (1%), and N=6 were symptomatic (6%).

The majority of symptomatic ARIA-H in the LEC10-BW-Treated Period was concurrent with ARIA-E. The most common symptoms were headache, dizziness, and confusional state.

All symptomatic ARIA-H events were mild or moderate for all genotypes in study 301 core, and distribution of severity remained overall consistent during 36 months of continuous treatment with 2 patients reporting severe symptomatic ARIA-H concurrent with ARIA-E, both of them being homozygous for APOE4, and one of them reported a seizure.

Given that ARIA-E cannot be predicted, nor mitigated, the proposed recommended monitoring is a baseline (within 6 months) brain magnetic resonance imaging (MRI), and a routine MRI prior to the 5th, 7th and 14th infusions. For any upcoming symptoms, additional MRIs should be considered according to section 4.2 and 4.4 of the SmPC.

ARIA-H stabilised more slowly in LEC10-BW arm than in placebo arm, with 11.1% and 23.7% of non-stabilised ARIA-H at first follow up MRI in the placebo group and for overall lecanemab. With regard to noncarriers and heterozygous carriers of APOE4, 14.4% of ARIA-H did not stabilise at first follow-up MRI.

Most cases of ARIA-H with PBO or LEC10-BW were ongoing at the end of Study 301 Core. All cases of macrohaemorrhage with PBO or LEC10-BW were ongoing, which was expected, as these events tend to not resolve, but at best stabilise.

Most subjects of the intended population experienced only one ARIA-H event, while 31 of 98 patients (32%) with ARIA-H experienced a recurrent event. Multiple events occurred, either symptomatic or asymptomatic. Recurrence of ARIA-H is addressed in the SmPC sections 4.2, 4.4, and 4.8.

Based on the overall data on ARIA-H, SmPC section 4.2 recommends continuing lecanemab if ARIA-H is asymptomatic and radiographically mild. Lecanemab should be interrupted if asymptomatic moderate ARIA-H or symptomatic mild or moderate ARIA-H occurs; a follow-up MRI 2 to 4 months after initial identification should be conducted to confirm radiographic stabilisation or resolving of symptoms. Lecanemab should be discontinued if asymptomatic or symptomatic severe ARIA-H occurs.

Seizures concurrent with ARIA occurred in a similar incidence for LEC10-BW (0.3%, 3 patients) and placebo (0.1%, 1 patient) in study 301 core. ARIA events in these patients resolved radiographically; one event resolved with sequelae of partial seizures with secondary generalisation. Two of the three patients with seizures and ARIA in the LEC10-BW group were homozygous for APOE4, one was heterozygous. Eight additional patients were reported with seizures with concurrent ARIA during 301 OLE. All except one patient were APOE4 carriers. Occurrence of seizures is labelled in the SmPC.

Intracerebral haemorrhage (ICH) > 1cm in diameter occurred throughout the treatment and with an incidence of 0.7% in the LEC10-BW group (6/898 patients; 0.0051 per PY of exposure) and of 0.2% in the placebo group (2/897 patients; 0.0016 per PY of exposure). The risk for ICH > 1 cm is higher in APOE4 homozygous carriers. In noncarriers and heterozygous carriers of APOE4, the incidence of ICH was 0.5% for LEC10-BW and 0.3% for placebo. Clinical severity appeared independent from genotype and was either mild, moderate, or severe. All ICH > 1 cm events in the LEC10-BW group were radiographically ongoing. Two events of ICH > 1 cm were fatal, amongst them, one in a homozygous APOE4 carrier and one in a noncarrier. Neither the incidence nor clinical severity of ICH > 1 cm were found to increase with longer treatment. Serious ICH occurred in 4 patients in 301 core (1 was a

homozygous APOE4 carrier). Symptomatic events of ICH > 1 cm solely occurred in the 301 Core period. Symptoms reported were dysarthria, hemiparesis, asthenia, speech disorder, behaviour disorder, headache, monoparesis and partial seizures. ICH, including monitoring and risks associated with concomitant CAA, as well as with the use of anticoagulants and thrombolytics is labelled in the SmPC. Lecanemab must be permanently discontinued if intracerebral haemorrhage greater than 1 cm in diameter occurs.

Fatal events associated with ARIA-E, -H, and ICH > 1 cm with lecanemab (n=3) solely occurred in the 301 OLE (contrasting a single fatal event with concurrent ICH>1 cm in the placebo group in a noncarrier subject in the 301 core study): one homozygous APOE4 carrier with multiple ICH>1 cm after tissue plasminogen activator (tPA); one noncarrier with subacute ICH > 1 cm; and one homozygous APOE4 carrier with severe ARIA-E and concurrent ARIA-H microhaemorrhage. Communalities of the three deaths were (1) first administration of lecanemab in the OLE of study 301; (2) occurrence within the known time-to-onset of ARIA events; (3) CAA, which is the most common risk factor for ICH; (4) concurrent treatment with antithrombotic medication at the time of the events (subject with apixaban and heparin; subject with ASA and heparin; subject with tPA).

6.5. Uncertainties and limitations about unfavourable effects

Even with the restricted population some uncertainties remain.

While ARIA-E and ARIA-H concurrent with ARIA-E occurred early during treatment, isolated ARIA-H and ICH > 1 cm have been observed throughout the treatment period. In the SmPC, after the 14th infusion of lecanemab (i.e. after 6 months) only a "periodic monitoring" is specified. Given that isolated ARIA-H and ICH > 1 cm can occur at any time during the treatment, vigilance is also needed after the first 6 months, which is - at present - not fully addressed by risk minimisation measures regarding an additional MRI after 52 weeks.

All of the three fatalities in the OLE of clinical study 301 concurrent with ARIA-E, -H, and ICH > 1 cm were treated with antithrombotic medication at the time of the events, which raises uncertainty with regard to concomitant use of these treatments with lecanemab. Study 301 core/OLE did not show a clear increase in the risk of ARIA-E and ARIA-H when lecanemab was administered to patients taking concomitant anticoagulant and / or antiplatelet agents neither for the overall population nor for the different APOE4 genotypes. However, 2 of 78 patients treated with lecanemab concomitantly with an anticoagulant alone or combined with an antiplatelet medication or aspirin (one heterozygous and one homozygous APOE4 carrier) had ICH>1 cm compared to none of 70 patients on placebo with concomitant treatment. Of note, one of the three death cases had multiple ICH>1 cm after tissue plasminogen activator following a cerebrovascular accident. A warning has been included in SmPC section 4.4 with regard to initiation of thrombolytics in patients treated with lecanemab and description of ICH in section 4.8. However, labelling revision is recommended to also include a contraindication for initiation of lecanemab in patients receiving ongoing anticoagulant therapy given that these patients are at an increased risk for macrohaemorrhage and taking into account that available data at present are scarce. Moreover, section 4.4 should likewise address the management of lecanemab in case of anticoagulants or thrombolytic medications to be administered in patients already treated, i.e. a dose pause should be considered.

Beyond the overall four death cases during clinical study 301 (one placebo-treated patient in the 301 core and 3 fatal events in the OLE), there were four death cases with ARIA and/or ICH reported in the postmarketing setting, with seizures preceding the fatal events but lacking a specific genotype pattern. It needs to be considered that postmarketing fatal events derive from spontaneous sources and information is scarce.

Uncertainty has been raised as to which extent the risk of ARIA (-E and -H) cumulates over time, i.e. with continuous treatment. The risk of recurrence was found to increase with the number of APOE4 alleles, consistent with the generally increased risk of ARIA with the number of APOE4 alleles. Even though, the duration of the studies was limited, ARIA re-occurred in several patients. In 79 lecanemab–treated subjects, treatment-emergent ARIA-E or ARIAH (microhaemorrhage or superficial siderosis) led to interruption of study treatment. 69 of 79 (87.3%) subjects re-initiated treatment with lecanemab. Of these, more than half (56.5%, 39/69) had additional treatment-emergent ARIA-E or ARIA-H (microhaemorrhage or superficial siderosis) after re-initiation of treatment. While most of these re-occurrences did not lead to discontinuation, the long-term cumulative effects remain unknown. This uncertainty will be further addressed as part of the proposed PASS study.

The long-term consequences of ARIA remain uncertain, however, a consistent negative effect on cognition in the first 18 months of treatment with lecanemab could not be identified. An increase in brain volume loss relative to placebo was observed with anti-β amyloid antibodies, including lecanemab. The clinical relevance of this observation is currently unclear, given the results on clinical and other biomarker endpoints in Study 301. To further characterise "acceleration of disease progression due to ARIA induced brain atrophy," the applicant has proposed to provide data from ongoing studies Study 301 OLE Phase and Study 303, as well as from an EU Lecanemab All-Patient Study (registry-based) that will measure progression to the next stage of AD, as well as ARIA occurrence.

As mentioned by the SAG, the burden of MRI monitoring and the implications of genetic testing for treatment eligibility have also been considered. However, it is maintained that these cannot be characterised as unfavourable or harmful effects, but rather as features of the treatment paradigm that patients may consider when deciding whether to undergo treatment with Leqembi. As such, these elements are not considered in the benefit-risk discussion.

6.6. Effects Table

Table 105. Effects table for Leqembi, indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (early Alzheimer's disease) in adult patients that are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (data cut-off: 31 Mar 2024)

Effect	Short Description	Unit	Lecanemab (LEC10-BW)	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
			LEC10-BW (N=723)	**PBO (N=743)**		
CDR-SB Noncarrier and heterozygous *APOE4* Carrier subpopulation 18 months	Noncarrier and heterozygous *APOE4* Carrier subpopulation: Change from baseline in the CDR-SB at 18 months		1.151 (0.087)	1.730 (0.085)	Post hoc analysis on restricted population Difference LEC10-BW vs PBO: **-0.535** 95% CI: -0.778, -0.293,	Core Study 301

Effect	Short Description	Unit	Lecanemab (LEC10-BW)	Placebo	Uncertainties/ Strength of evidence	References
ADAS-Cog14 Noncarrier and heterozygous *APOE4* Carrier subpopulation 18 months	Noncarrier and heterozygous *APOE4* Carrier subpopulation: Change from baseline in the ADAS-Cog14 at 18 months		4.389	5.901	Post hoc analysis on restricted population Difference LEC10-BW vs PBO: **-1.512** (95%CI : -2.486, -0.538)	Core Study 301
ADCS MCI-ADL Noncarrier and heterozygous *APOE4* Carrier subpopulation 18 months	Noncarrier and heterozygous *APOE4* Carrier subpopulation: ADCS MCI-ADL Change from baseline in the 14 at 18 months		-3.873	-5.809	Post hoc analysis on restricted population Difference LEC10-BW vs PBO: **1.936** (95%CI : 1-029, 2.844)	Core Study 301
Unfavourable Effects						
			Lecanemab (LEC10-BW) **N=757 (Noncarriers and heterozygous carriers)**	**Placebo** **N=764 (Noncarriers and heterozygous carriers)**		
Symptomatic ARIA-E	Incidence in the Noncarrier and heterozygous *APOE4* Carrier subpopulation	%	1.6%	0%		Study 301 core
ARIA-H	Incidence in the Noncarrier and heterozygous *APOE4* Carrier subpopulation	%	12.9%	6.8%	Isolated ARIA-H occurs throughout the treatment period questioning the need for an additional MRI beyond 6 months.	Study 301 core

Effect	Short Description	Unit	Lecanemab (LEC10-BW)	Placebo	Uncertainties/ Strength of evidence	References
Intracerebral haemorrhage >1 cm	Incidence in the Noncarrier and heterozygous *APOE4* Carrier subpopulation	%	4/757 (0.5%)	2/764 (0.3%)	ICH > 1 cm occurs throughout the treatment period questioning the need for an additional MRI beyond 6 months. Increased risk of ICH>1 cm with anticoagulant and / or antiplatelet agents; uncertainty with regard to the risk of ongoing anticoagulant treatment	Study 301 core
Seizures associate with ARIA	Incidence in the Noncarrier and heterozygous *APOE4* Carrier subpopulation	%	1/757 (0.1%)	1/764 (0.1%)		Study 301 core

Abbreviations: AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14 item version, ADNI = Alzheimer's Disease Neuroimaging Initiative, APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality- haemorrhage, CDR-SB = Clinical Dementia Rating-Sum of Boxes, ITT = intent to treat, LEC10-BW = lecanemab 10 mg/kg biweekly, PBO = placebo.

Notes: Noncarrier and heterozygous APOE4 Carrier subpopulation analyses are post-hoc analyses; ARIA-H is defined as events of superficial siderosis or cerebral microhaemorrhage.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The confirmatory evidence comes from a single pivotal trial in a sufficient number of AD patients.

Efficacy has been sufficiently demonstrated in the overall study population. Efficacy in the restricted population of APOE4 non-carriers and heterozygous patients is consistent with this with an estimated treatment effect in the primary endpoint on CDR-SB scale over 18 months of 0.535 (95% CI: (0.293, 0.778)), corresponding to 33.5% less decline with LEC10-BW compared to PBO.

While statistically significant, the observed effects in the main clinical outcomes for the overall population were considered small. A discussion of the minimal clinically important change in CDR-SB, the primary endpoint, and in ADAS-Cog14, the first key clinical endpoint is a matter of ongoing debate. The statistical significance of the primary endpoint has already been acknowledged, and the clinical meaningfulness is supported by additional analyses for progressors and delay in progression time to event analyses as well as favourable effects in patient reported outcomes.

Key clinical secondary endpoints (ADAS-Cog14 and ADCS-MCI-ADL) supported the primary endpoint in favour of LEC10-BW for the restricted Noncarrier and Heterozygous APOE4 Carrier Population.

The model-based time-saved analyses suggest that the placebo group reached the 18-month level of decline in CDR-SB of the LEC10-BW group 6.1 months earlier. The effect size was slightly larger than in the overall population indicating that the results were not driven by the homozygous population. There is currently no biologically plausible explanation for the apparent lack of efficacy in the homozygous APOE4 carriers.

The majority of the various analyses indicate a risk reduction of 34% to progress to the next stage of AD with LEC10-BW in the Noncarrier and Heterozygous APOE4 Carrier Population. These findings are indicating relevant changes to patients and their ability to think and function.

Although without randomised control, the 36 months results of the delayed-start phase indicate that the trajectories in the decline continue to stay separated. When read in accordance with the applicable Guidelines on the clinical investigation of medicines for Alzheimer's disease (CPMP/EWP/553/95 Rev.2), this supports the notion that the benefit may not be merely symptomatic.

The safety profile of lecanemab is driven by the frequent occurrence of IRR and ARIA (-E and –H) events, which is a known class effect of anti-amyloid treatment (Yadollahikhales and Rojas, 2023). Serious clinical consequences of ARIA (including seizures and macroscopic intracerebral haemorrhage) are uncommon in the overall study population, and there was no substantial difference in mortality between the treatment arms in the clinical studies (PBO (7/897 [0.8%]) and LEC10-BW (6/898 [0.7%])). In total, four death cases with ARIA and/or ICH have been reported postmarketing, with seizures preceding the fatal events but lacking a genotype pattern. It needs to be considered that the postmarketing fatal events derive from spontaneous sources and information is scarce. A category 1 PASS (an EU Lecanemab All-Patient Study, registry-based) will be in place to address this uncertainty.

The now proposed indication for lecanemab accounts for the fact that the risk of ARIA-E and ARIA-H was found highest in homozygous APOE4 carriers and comprises only heterozygous and noncarriers of APOE4.

ARIA events were mostly asymptomatic and of radiographically mild or moderate severity; however, serious and symptomatic ARIA occurred more frequently in homozygous APOE4 carriers as compared to noncarriers and heterozygous APOE4 carriers. Symptomatic ARIA mainly presented with headache, confusional state, dizziness, and nausea; cerebral macrohaemorrhages and seizures rarely occurred as severe presentation. Postmarketing data (from markets where the unrestricted population is eligible for treatment with lecanemab) contribute to the finding that seizures can occur in patients presenting with ARIA and lecanemab treatment. Events of ICH have been reported in the postmarketing setting but background information is scarce. Overall, the postmarketing data mainly from the US market and covering approximately 18 months of treatment appear to be in line with the clinical study data with regard to the time-to-onset and severity of events, the involvement of APOE4 carriers, the concurrent appearance of ARIA-H with ARIA-E, and the symptoms reported (including seizures).

Patients with Alzheimer's disease can have several risk factors that predestine them for ARIA events or ICH >1 cm, i.e. higher age, APOE4 carrier status, a history of stroke or cerebral microhaemorrhages, antithrombotic/ anticoagulant use, and vascular risk factors. Therefore, determination of eligibility for treatment with lecanemab is crucial and appropriate risk minimisation including monitoring and management of ARIA need to be applied.

The most important risk factor for ARIA especially in patients treated with anti-amyloid treatment is the APOE4 homozygous genotype that predisposes patients for ARIA being more likely symptomatic and severe as compared to noncarriers and heterozygous APOE4 carriers (Doran et al., 2024). Based on the study 301 core data, homozygous APOE4 carriers were found almost 3-times as likely to suffer

from total ARIA-E and ARIA-H events, and 5-times as likely to suffer from symptomatic ARIA-E and SAEs of ARIA-E compared to heterozygous APOE4 carriers. The incidence of ICH was found twice as high for homozygous carriers as compared to heterozygous carriers of APOE4.

Thus, restricting the indication to noncarriers and heterozygous carriers of APOE4 as proposed by the applicant is reasonable to further reduce the risk of

- severe, serious and symptomatic ARIA,
- seizures, since seizures are expected to occur more frequently in patients with severe and serious ARIA.
- ICH > 1 cm, which was highest in the homozygous APOE4 carriers (LEC 10 mg /kg BW: 1.4%) versus 0 in the placebo group. In the now proposed patient population (noncarriers and heterozygous APOE4 carriers), 4 patients (0.5%) had TEAEs of ICH > 1 cm; thus, the incidence is considered to remain within the placebo rates from AD trials, which is (0.4% - 1%) over 18 months as reported by Honig et al. (2024).
- ARIA recurrence, as this depends on the number of APOE4 alleles, consistent with the generally increased risk of ARIA with the number of APOE4 alleles.

ARIA is related to the presence of amyloid in cerebral blood vessels walls (cerebral amyloid angiopathy; CAA) in patients with AD. Existing cerebral microhaemorrhages are a risk factor for developing significant ARIA-E and ARIA-H with lecanemab, which aims at the removal of amyloid. Moreover, the APOE4 allele can predict severe CAA (Ringman, et al., 2014).

CAA was confirmed (suspected) to be involved in two (one) of the three fatal cases related to ARIA and/ or ICH in the 301 OLE study, and 2 of the 3 patients were APOE4 homozygous carriers. One of the two subjects additionally received antithrombotic medication (tPA) for cerebrovascular accident. The sum of risk factors in this patient is considered a worst-case scenario, which will be avoided with the RMMs delineated in the product information:

Section 4.3 of the SmPC accounts for the risk of severe CAA excluding patients with MRI findings of >4 microhaemorrhages or an area of superficial siderosis on pre-treatment MRI, which is considered adequate to address this risk.

In addition, antithrombotic use is a significant risk factor for developing ARIA-H and ICH (macrohaemorrhages) (Doran et al., 2024). The measures proposed in the SmPC, including a warning in section 4.4 with regard to initiation of thrombolytics in patients treated with lecanemab and description of ICH in section 4.8 are considered to address this risk, while AD patients with ongoing anticoagulant treatment are not considered to be sufficiently covered by the present RMMs given that the data on concomitant anticoagulant treatment are scarce and resulted in 2 (APOE4 carrier) patients with intracerebral haemorrhage. Therefore, a contraindication for ongoing anticoagulant treatment has been included in section 4.3.

It needs to be mentioned that there were three additional fatal cases in the postmarketing setting in patients who experienced ARIA-E, including 2 reports of concurrent ARIA-E and ARIA-H, all from spontaneous sources in the US. There was also a single fatal spontaneous post-marketing report of ICH> 1 cm from the US. Autopsy in these death cases was either not performed or unknown to have been performed. Two of the fatal events have been considered as possibly related to lecanemab by the reporting HCP.

The post-hoc restriction to the non-carrier and heterozygous APOE4 subgroup is also justifiable from an efficacy perspective since the results were not driven by the homozygous population and even seem to be more favourable than in the Overall population.

The proposed Controlled Access Programme further reassures on the strict adherence to certain RMMs, which is regarded as necessary for the safe use of Leqembi. Furthermore, a EU registry will be set up and an all-patient EU study (category 1 PASS) performed.

In summary, the restricted indication with exclusion of homozygous APOE4 carriers from treatment with lecanemab, together with application of additional risk minimisation measures is considered appropriate to reduce the risk of severe and symptomatic ARIA and its consequences for patients treated with lecanemab in clinical practice. Moreover, the additional measures, including Healthcare Professional Guide and Checklist, patient alert card, follow-up questionnaire, trainings programmes for ARIA and educational material, as well as a PASS study to evaluate drug utilisation and prove the effectiveness of these measures, are considered extensive and appropriate to address the risk of ARIA and ICH with lecanemab treatment postmarketing. The proposals for risk minimisation measures and additional pharmacovigilance by the applicant will also be able to provide additional information for the extensively explored long-term consequences of ARIA and brain volume differences.

6.7.2. Balance of benefits and risks

Overall, the benefit-risk balance of lecanemab is considered favourable for a restricted population of Noncarrier and Heterozygous APOE4 carriers.

The provided post-hoc analyses are in support of a better safety and at least comparable efficacy profile in this restricted population compared to the originally proposed population including APOE4 homozygous carriers.

The incidence of severe, serious and/ or symptomatic ARIA events and their consequences is acceptably low when excluding homozygous APOE4 carriers. The safety profile of lecanemab is considered acceptable in the newly proposed restricted indication taking into account further safety measure in the product information together with the extensive additional pharmacovigilance measures proposed in the postmarketing setting, which include a category 1 PASS (EU Lecanemab All-Patient Study, registry-based).

The CHMP therefore considers that, efficacy and safety of lecanemab has been sufficiently demonstrated in the noncarrier and heterozygous APOE4 carrier population.

6.8. Additional considerations on the benefit-risk balance

6.8.1. Third-Party Interventions

Several letters have been sent to the European Medicines Agency, almost unanimously supporting the approval of Leqembi. The senders include healthcare professionals, including European Neurological, Psychiatric or Alzheimer's associations, advocacy associations and individual patients or family members of patients.

Specific aspects raised in the above mentioned third party interventions were:

- The unmet need in the face of an inexorable and deeply invalidating disease;
- Primary and secondary endpoints were met in clinical trials, with significant slowing of disease progression and meaningful benefits observed in cognitive and functional decline, improving quality of life for patients and caregivers;

- Postmarketing safety data show that the risks are manageable in a real world setting with appropriate patient selection and monitoring;
- Offers for support for post-marketing safety studies and registries to monitor long-term safety and effectiveness;
- Patient surveys that – while hampered by methodological limitations and insufficient specification of the methods – can be interpreted as supporting the meaningfulness of the efficacy profile described.

6.9. Conclusions

The overall benefit/risk balance of Leqembi is positive subject to the conditions stated in section 'Recommendations'.

Divergent positions are appended to this report.

7. Recommendations following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Leqembi is favourable in the following indication:

> *Lecanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (see section 4.4).*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, sections 4.2 and 4.4).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State prior to Leqembi being marketed, all healthcare professionals and patients who are expected to prescribe or use Leqembi have access to/are provided with the following educational package which should be agreed with the National Competent authorities of those member states:

- *Guide for healthcare professionals*

The Guide for healthcare professionals should contain the following key elements:

- Statement outlining there is a controlled access programme.
- Statement that all EU lecanemab patients must be registered in the registry and brief information on how to enrol patients.
- Contraindications.
- Information on ARIA, including what it is, incidence and symptoms (ARIA-E and ARIA-H (microhaemorrhages and superficial siderosis).
- ARIA Intracerebral haemorrhage >1 cm in diameter including what it is, incidence, and use of concomitant antithrombotic medication.
- Activities to be undertaken prior to treatment including baseline MRI and *APOE4* testing.
- How to identify and manage ARIA through MRI monitoring, radiographic severity criteria, and the treatment recommendations (can be adjusted based on the national clinical practice).
- Patients who are homozygous *APOE4* carriers have a higher incidence of ARIA when treated with monoclonal antibodies directed against aggregated forms of Aβ, including lecanemab, compared to heterozygous *APOE4* carriers and noncarriers. Lecanemab is not indicated for use in homozygous *APOE4* carriers.
- Statement that ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke.
- Package Leaflet and Patient Card must be given to the patient/caregiver.
- Reminder of how and where to report side effects.
- Lists of tests to be conducted for the initial screening of the patient:
    - The patient has a clinical diagnosis of MCI due to Alzheimer's disease or Mild Alzheimer's disease, including the presence of amyloid beta pathology. A recent (within 6 months) baseline brain MRI has been obtained prior to initiating treatment with Leqembi.
    - *APOE* ε4 (gene) (understanding *APOE* ε4 genotype is important to identify appropriate patients to treat).
    - No findings suggestive of CAA on pre-treatment MRI.
    - Organisation of appointments of follow up MRI scans.

- *Patient Card*

The Patient Card should contain the following key elements:

- Request to read the package leaflet.
- Summary of what Leqembi is used for.
- Information that treatment with Leqembi should not be initiated in patients receiving ongoing anticoagulant therapy.
- Information on how Leqembi is administered, time management of administration and information about the need and number of MRI scans.
- A warning message for physicians treating the patient at any time, including in conditions of emergency, that the patient is using lecanemab.
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional.

- *Controlled Access Programme*

The MAH shall agree to the details of a Controlled Access Programme with each National Competent Authority and must implement such programme nationally to ensure that a Controlled Access Programme (CAP) promotes the safe and effective use of lecanemab and prevents off-label use.

The Controlled Access Programme includes the following key principles that will be incorporated within each system in all Member States. These are:

- Each HCP will be registered separately before they are able to enrol patients in the CAP. As part of the HCP registration process, HCPs will be required to confirm that they have been provided with and understand the Guide for Healthcare Professionals and the SmPC and that they meet requirements to comply with the restricted medicinal prescription status (described in the section 4.2 of the SmPC).
- Treatment in all patients should be initiated through an imposed central registration system. The system will ensure appropriate and relevant information on the specified data fields (such as amyloid pathology, MCI or mild AD, *APOE4* genotype, MRI, history of cerebral haemorrhage, anticoagulant therapy, patient card and PIL, acknowledgment of risks) prior to the first infusion of lecanemab, for all patients.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
EU Lecanemab All-Patient Study	Draft protocol: January 2025 Final protocol: March 2025 Progress Reports: Annually starting September 2026

Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lecanemab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

8. Appendices

8.1. Divergent position(s) to the majority recommendation

The undersigned members of the CHMP did not agree with the CHMP's majority positive opinion recommending the granting of a Marketing Authorisation for lecanemab in the treatment of mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease (AD) (Early Alzheimer's disease) in adult patients that are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology.

The unmet need for a treatment of Alzheimer's disease is fully acknowledged, and currently no disease-modifying medical treatments for AD are available in the EU. However, the reasons for the

divergent - negative - opinion were as follows:

- The evidence in this MAA comes from a single pivotal study with no clear confirmation of the surrogacy value of the biomarker. With a single pivotal trial, results are expected to be particularly compelling with respect to clinical relevance, and not only statistical significance. There is a strong need to have a clear demonstration that targeting existing cerebral amyloid can delay the progressive disease course of AD in terms of both cognition and function, which is not convincingly demonstrated in this case.
- In the restricted population excluding ApoE ε4 homozygous patients the effect size (change in CDR-SB: -0.54 [95%CI;-0.77,-0.30]) is considered limited , similar to the effect seen in the overall population initially applied for (that included the ApoE ε4 homozygous patients). The clinical relevance of these findings remains uncertain. On a group level, the placebo and lecanemab treated patients both crossed the minimum clinically important difference (MCID) that are reported in literature for the different outcomes and had thus meaningful disease progression (deterioration) on a group level.
- A Scientific Advisory Group (SAG), consisting of clinical experts and patient representatives, indicated that the effect sizes in the single study were not of clinical relevance. The SAG also noted that mandatory APoE4 testing for eligibility for treatment could raise ethical concerns for the relatives and offspring.
- Although the ApoE ε4 homozygous patients were excluded from the target population, the incidence of ARIA in the restricted population is still substantial, with ARIA events occurring very commonly (all ARIA: 16.9% [ARIA-E: 8.9%, ARIA-H: 12.9%]). Although most patients experience an asymptomatic, and radiographically mild to moderate ARIA event, a significant number of patients experience serious (0.8%) and/or symptomatic ARIA (~2.0%), including seizure and intracerebral haemorrhage (ICH).
- Most worrisome, fatal events in the context of treatment-related ARIA and/or ICH occurred, also within the restricted population. These most harmful events cannot be fully prevented, despite the extensive risk minimisation measures proposed.
- The proposed controlled access programme (CAP) may help health care professionals to adhere to certain risk minimisation measures, e.g., select the correct patients (ApoE ε4 status of the patient and lack of contra-indications of the product) and inform patients about the risks, but it does not change the risks seen with lecanemab; even when RMMs are applied correctly, a substantial group of patients in the target population still experiences ARIA, including fatal events. The proposed registry-based study may provide post-approval information on (long-term) patient safety, and shifts in AD stage of treated patients, but will be difficult to interpret if only treated patients are monitored. Furthermore, the study will not help minimise the risks.
- The post-marketing safety observations strengthen the concern to what extent ARIA will be recognised and handled outside the setting of a controlled clinical trial. ARIA occurrence and consequences may be more severe in clinical practice, e.g., when there are challenges with the full implementation of the proposed risk minimisation measures (among others, genetic testing, periodic monitoring MRIs), or when the treated population has more co-morbidities (including concurrent medications).
- Regarding long-term safety, although ARIA-E (oedema) typically resolves over time, the consequences of successive and/or more severe ARIA-H (haemorrhage) are much less clear, as they usually do not resolve radiographically. ARIA-H is associated with an increased risk of subsequent ARIA, including ICH, and clinical effects may present specifically on the longer term. In general, also triggered by observations of increased brain volume loss with anti-amyloid therapies that appear not solely attributable to amyloid removal, long-term consequences of ARIA and/or anti-amyloid antibody therapies remain to be elucidated.

To conclude, the limited effects achieved with lecanemab treatment do not outweigh the risk of potentially fatal events of ARIA in a population of ApoE ε4 non-carriers and heterozygous MCI and mild dementia due to AD patients. Therefore, it is the opinion of the divergent CHMP members that the benefit-risk balance of Leqembi is negative.

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