16 December 2021
EMA/CHMP/557556/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Aduhelm

International non-proprietary name: aducanumab

Procedure No. EMEA/H/C/005558/0000

Note

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

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List of abbreviations

Aβ	β amyloid (peptide derived from membrane-bound amyloid precursor protein)
AD	Alzheimer's disease
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items)
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody dependent cell-mediated phagocytosis
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version)
ADU	aducanumab
AET	analytical evaluation threshold
AEX	anion exchange chromatography
ApoE ε4	apolipoprotein E4 ε4
ARIA	Amyloid Related Imaging Abnormality
AUC	analytical ultracentrifugation
BSE	bovine spongiform encephalopathy
CCP	critical controlled parameter
CDC	complement-dependent cytotoxicity
CDR	complementarity-determining region
CDR-SB	Clinical Dementia Rating sum of boxes
CE-SDS	capillary electrophoresis in the presence of sodium dodecyl sulfate
CEX	cation exchange chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CIPC	critical in-process control
CIPT	critical in-process test
CQA	critical quality attributes
CSR	clinical study report
CV	column volumes
Da	daltons
DMT	disease modifying therapy
DNA	deoxyribonucleic acid
DP	drug product
DS	drug substance

DSC	differential scanning calorimetry
EMA	European Medicines Agency
EQ-5D	EuroQol health status measure
ESI-MS	electrospray ionization mass spectrometry
ETFE	ethylene tetrafluoroethylene
ETTI	equal tail tolerance interval
EU	European Union
FDA	Food and Drug Administration
FTIR	Fourier transform infrared
GMP	Good Manufacturing Practice
HC	heavy chain
HCCF	harvested cell culture fluid
HCP	host cell proteins
HCP	health care professional
HDX-MS	hydrogen/deuterium exchange mass spectrometry
HIC	hydrophobic interaction chromatography
HILIC	hydrophilic liquid chromatography
HMW	high molecular weight
HPLC	high performance liquid chromatography
icIEF	imaged capillary isoelectric focusing
ICP-MS	inductively coupled plasma mass spectrometry
IPC	in-process control
ISE	Integrated Summary of Effectiveness
ITT	intent-to-treat
IV	intravenous
LC	light chain
LMW	low molecular weight
LOAEL	lowest observed adverse effect levels
LTE	long-term extension
MAA	Marketing Authorisation Application
MALS	multiangle light scattering
Man5	Mannose 5
MCB	master cell bank

MCI	mild cognitive impairment
MIA	Manufacturing and Importation Authorisation
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MMV	Mouse Minute Virus
MoA	mechanism of action
mPDQ-20	Perceived Deficits Questionnaire-20 modified version
MRI	magnetic resonance imaging
MMV	Mouse Minute Virus
MoA	mechanism of action
NPI-10	Neuropsychiatric Inventory-10
OOS	out-of-specification
PC	placebo-controlled
PET	positron emission tomography
pI	isoelectric point
PK	pharmacokinetic(s)
PRS	primary reference standard
PRV	Pseudorabies
PS80	polysorbate 80
QP	Qualified Person
Reo-3	Reovirus serotype 3
RH	relative humidity
ROI	region of interest
RS	reference standard
SAR	structure-activity relationship
SEC	size exclusion chromatography
SmPC	Summary of Product Characteristics
SPTFF	single pass tangential flow filtration
SUVR	standard uptake value ratio
TSE	transmissible spongiform encephalopathy
TTC	threshold for toxicological concern
UBH	unprocessed bulk harvest
UF/DF	ultrafiltration/diafiltration

UV	ultraviolet
WCB	working cell bank
WFI	water for injection
WRS	working reference standard
X-MuLV	Xenotropic Murine Leukemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Netherlands B.V. submitted on 7 October 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Aduhelm, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "disease modifying treatment in adult patients with Alzheimer's disease at the mild cognitive impairment (MCI) or mild dementia stage. Presence of amyloid beta pathology should be confirmed as part of diagnosis".

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(s) 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.

1.5. Substance status

The applicant requested the active substance aducanumab 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.

1.6. PRIME

Aduhelm was granted eligibility to PRIME on 26 May 2016 in the following indication: treatment of Alzheimer's Disease.

Eligibility to PRIME was granted at the time in view of the presence of an unmet need in Alzheimer's Disease and of the results – both on the primary and on the main secondary endpoints – of study 103.

Upon granting of eligibility to PRIME, Luca Pani was appointed by the CHMP as rapporteur. In 2017, Jan Mueller-Berghaus was appointed as the replacement rapporteur.

A kick-off meeting was held on 12 September 2016. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures: quality aspects, aspects of the phase 3 trial (duration and interim analysis), and post-approval development.

PRIME eligibility was withdrawn on 5 June 2019 at the request of the applicant in view of the discontinuation of the Phase 3 trials with aducanumab, in mild cognitive impairment (MCI) and mild AD.

1.7. 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**
26 February 2015	EMEA/H/SA/2982/1/2014/III	Fernando de Andrés Trelles, Valentina Mantua
14 September 2017	EMEA/H/SAH/083/1/2017/PR/II	Valentina Mantua, Mario Miguel Rosa
14 December 2017	EMEA/H/SA/2982/2/2017/PR/I	Jan Mueller-Berghaus, Valentina Mantua
26 July 2018	EMEA/H/SA/2982/4/2018/HTA/PR/II	Fernando de Andrés Trelles, Elena Wolff-Holz
27 July 2018	EMEA/H/SA/2982/3/2018/PR/I	Elena Wolff-Holz, Christian Gartner

The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- EMEA/H/SA/2982/1/2014/III
    - Quality: Comparability of manufacturing processes;
    - Non-clinical: Acceptability of the non-clinical package;
    - Clinical: Eligibility criteria, primary and secondary endpoints for the phase 3 studies, demonstration of disease-modification, dose selection, overall clinical package and safety monitoring.
- EMEA/H/SAH/083/1/2017/PR/II
    - Clinical: Statistical and operational aspects of interim analysis, statistical analysis plan, plans for post-authorisation evidence generation.
- EMEA/H/SA/2982/2/2017/PR/I
    - Quality: Comparability of Manufacturing processes, stability data, addition of manufacturing sites.
- EMEA/H/SA/2982/4/2018/HTA/PR/II

- Clinical: Plans for post-authorisation evidence generation.

- EMEA/H/SA/2982/3/2018/PR/I
  - Quality: Control Strategies for Drug Substance and Drug Product.

1.8. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	7 October 2020
The procedure started on	29 October 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 February 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 May 2021
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	28 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 October 2021
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	27 October 2021
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.	29 October 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	09 November 2021
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 Aduhelm on	16 December 2021

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. Initial impairment in memory and executive dysfunction may be followed by behavioural and neuropsychiatric symptoms. In conjunction, a person's ability to perform usual daily life activities declines. The observed decline in cognitive measures typically precede those seen on functional measures, especially in the early symptomatic stages [Liu-Seifert 2018], yet these two become increasingly co-contributory as the patient's progress in overall disease severity [Liu-Seifert 2016; Liu-Seifert 2018].

AD is characterised biologically by two hallmark proteinopathies: extraneuronal amyloid plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein [Vermunt 2019]. Abnormal protein deposition occurs over decades and is followed by neurodegeneration and significant subsequent cognitive decline, ultimately leading to death [Vermunt 2019].

2.1.2. Epidemiology and risk factors

Alzheimer's Disease International estimates that as of 2018, there were about 50 million people living with dementia worldwide and that this figure may increase to 152 million by 2050 [Alzheimer's Disease International 2018]. AD is the most commonly diagnosed form of dementia, accounting for an estimated 60% to 80% of cases [Alzheimer's Association 2020; Rizzuto 2012; Winblad 2016]. In a 2017 meta-analysis of AD in Europe, the prevalence of AD increased from an estimated 1% in ages 65 to 74 years to 8% in ages 75 to 84 years and 23% in ages over 85 years, although heterogeneity across studies was high [Niu 2017].

AD and other dementias were estimated to be the third leading cause of death in Europe among individuals 70 years and older, with approximately 640,000 deaths attributable to dementia in this age group in 2017 [Ritchie 2019a]. According to mortality statistics from the UK, AD and other dementias are the leading cause of death in women and the second leading cause of death in men [Dementia Statistics Hub 2020]. Globally, estimates for AD as the underlying cause of death ranged from 1.4 to 1.9 million in 2016 [GBD 2016 Dementia Collaborators 2019].

The most salient known risk factors for AD are unmodifiable factors as older age, genetics, and family history. Of these, increasing age has the largest known impact on the risk of developing AD, and the incidence of AD is approximately 10 fold higher in European populations aged over 85 years compared with those aged 65 to 74 years [Niu 2017]. While several genes have been found to increase the risk of AD, the ε4 allele of the apolipoprotein E (ApoE) gene is the strongest known genetic risk factor [Alzheimer's Association 2020]. Compared with the most common ApoE genotype of ε3/ε3, ε4 heterozygosity increases the risk of AD by 3 to 4 times, and ε4 homozygosity increases risk by 10 to 15 times. Approximately 66% of biomarker-confirmed AD cases are ε4 positive, compared with a prevalence of about 15% to 20% in the general population [Mattsson 2018]. Autosomal dominant genetic mutations (APP, PSEN1 and PSEN2) are estimated to account for less than 1% of AD cases [Bekris 2010].

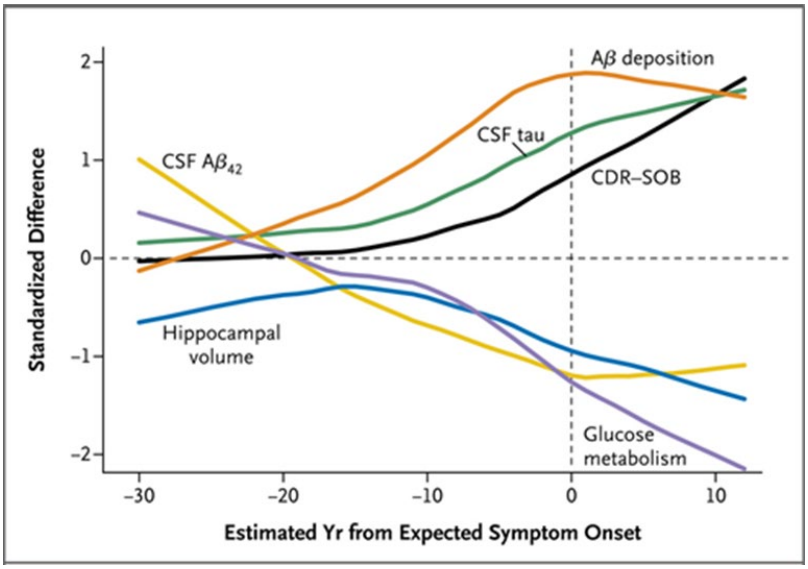
2.1.3. Aetiology and pathogenesis

The pathogenesis of AD, including the contribute of plaques and tangles to the clinical syndrome remains to be fully elucidated. The "amyloid cascade hypothesis" – relevant for this development - proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain [Hardy and Selkoe 2002].

Genetic evidence supports the amyloid hypothesis, and in the autosomal dominantly inherited forms of AD have mutations that have an impact on the generation or on the clearance of Aβ. In particular, the APP gene is the precursor of the Aβ peptide, which is produced upon sequential enzymatic cleavage by β and γ secretases. The presenilin1 and presenilin2 proteases were identified as two catalytic subunits of the γ-secretase complex.

Deposition of Aβ is followed sequentially by markers of neurodegeneration [Vermunt 2019]: accumulation of tau pathology [Hanseeuw 2019] and brain volume loss [Villemagne 2013], all of which initiate prior to the onset of clinical symptoms. Once symptoms are present, progression of cognitive impairment, as measured by CDR-SB, correlates closely with markers of neurodegeneration, and not with Aβ deposition (Figure 1 [Bateman 2012]).

Figure 1: Comparison of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes as a Function of Estimated Years from Expected Symptom Onset



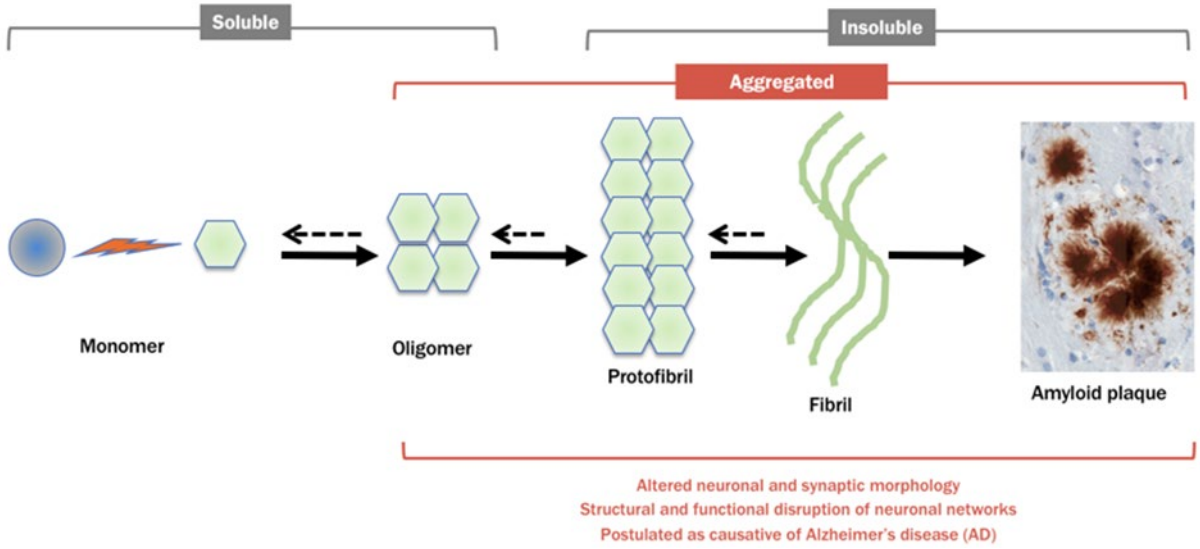
Source: [Bateman 2012]

Based on the assumption that the accumulation of Aβ in the brain is the primary driver of the disease process, targeting Aβ early in the disease course might be a viable method to interrupt the further cascade of toxic protein deposition and the neural degeneration that ultimately lead to cognitive impairment. However, the timing of Aβ removal might be a critical factor, as it has been postulated that there is a point – correlated with the manifest clinical deficits - at which the neurodegeneration becomes irreversible [Gómez-Isla 1996; Long and Holtzman 2019].

Sequential proteolytic cleavage of the APP protein by β- and γ-secretases leads to the production of Aβ peptides (monomers), mostly of lengths between 39 and 43. Multiple studies have demonstrated that, upon the accumulation of these hydrophobic Aβ peptides, an aggregation phenomenon will occur and

lead to the formation of different Aβ species defined by their size and structure. Following well-characterised biophysical reactions, Aβ monomers will aggregate into small and large oligomers, then fibrils. Aggregation and deposition of fibrils will, in turn, lead to the formation of amyloid plaques in the brain (Figure 2).

Figure 2: Description of the amyloid species and their aggregation



While the exact nature of the relevant pathological Aβ species remains to be elucidated, experimental evidence suggests that aggregated forms of Aβ, including soluble oligomers and amyloid plaques, can be synaptotoxic and neurotoxic [Koffie 2009; Kuchibhotla 2008; Meyer-Luehmann 2008], while monomers are not considered to exhibit these detrimental properties. A direct detrimental effect of Aβ fibrils deposited into amyloid plaques on morphology and function of neighbouring axons has also been demonstrated, and amyloid plaques were shown to act as a reservoir of synaptotoxic oligomers [Benilova 2012; Kayed and Lasagna-Reeves 2013]. Inflammatory reactions involving microglia and astrocytes have been described in the vicinity of amyloid plaques [Frost 2019]. Since its introduction, the amyloid cascade hypothesis has been widely embraced. However, this hypothesis is also under discussion, also triggered by the numerous failed RCT's of treatments based it.

2.1.4. Clinical presentation, diagnosis and prognosis

Current understanding of AD describes a biological and clinical continuum, extending from preclinical phases of disease evidenced only by neuropathology without clinical symptoms, through the early symptomatic phases (e.g., MCI due to AD / prodromal AD / Stage 3), and ultimately dementia due to AD [Jack 2018]. Sometimes, patients with mild Dementia due to AD and patients with MCI due to AD/prodromal AD/Stage 3 are collectively referred to as "early AD". Disease staging in this sense may be useful to describe clinical severity in the context of clinical trials; however, the disease itself is viewed as a continuous process rather than in distinct clinical stages [Aisen 2017]. Furthermore, the cognitive and functional changes that define AD may be similarly thought of as co-existing on a spectrum of cumulative clinical decline rather than as dichotomous assessments or distinct pathophysiologic processes.

Life expectancy after an AD diagnosis depends on various factors, including age at onset and severity at diagnosis [Brodaty 2012; Guehne 2007; Guehne 2005; Xie 2008]. For individuals diagnosed in the early

stages of the disease, a relatively longer life expectancy of 10 to 20 years or more may be possible; however, clinical studies indicate that approximately 50% to 60% of these early and symptomatic AD patients will progress to overt dementia within 3 years [Vos 2015]. About half of the remaining years of life of patients diagnosed with AD are spent in the severe disabling disease state [Rizzuto 2012]. That is, rather than just the mortality, it is the severe morbidity — the insidious loss of the ability to continue to live as one's known self and by one's own self — that devastates individuals with AD, their care partners, families, and communities.

2.1.5. Management

Licensed treatment options for patients with mild to moderately severe AD are the cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and, for patients with moderate to severe AD, the N-methyl-D-aspartate antagonist, memantine. These agents provide symptomatic benefit only, and for a limited duration of effect due to the continued progression of the disease process [Birks 2006; McShane 2006].

There are no approved medications available for patients with earlier stages of the disease, e.g., MCI due to AD /prodromal AD (consistent with Stage 3 and Stage 4 AD) [Jack 2018]. However, there is some evidence that supports the use of these medications in the MCI due to AD /prodromal AD population [Petersen 2005]. Risperidone is approved for short-term treatment of persistent aggression in patients with moderate to severe AD. No new medicines for AD have been introduced in the EU for over 15 years.

2.2. About the product

Aduhelm contains Aducanumab active substance which is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody that specifically binds to soluble and insoluble aggregated forms of human amyloid-beta (Aβ).

The drug product is Aducanumab 100 mg/ml concentrate for solution for infusion. Formulation buffer contains 16.2 mM L-histidine hydrochloride monohydrate, 3.8 mM L-histidine, 150 mM L-arginine hydrochloride, 10 mM L-methionine, 0.05% (w/v) polysorbate 80 and water for injection QS to final volume. The product is intended for intravenous infusion. The product is supplied in a Type I glass vial closed with a stopper and seal with a flip-off cap. The drug product is manufactured in seven different presentations differing in filling volume (170 mg, 300 mg, 450 mg, 600 mg, 750 mg, 850 mg and 1000 mg). The vials each contain a single dose of the drug product.

Biogen has developed aducanumab as a disease-modifying treatment to delay clinical decline in patients with AD. The claimed indication is "Aduhelm is indicated as a disease-modifying treatment in adult patients with Alzheimer's disease at the mild cognitive impairment (MCI) or mild dementia stage. Presence of amyloid beta pathology should be confirmed as part of diagnosis".

The observation underlying the development of aducanumab was that healthy elderly individuals, or patients with cognitive impairment but stable in the course of their disease, showed an immune response and generating antibodies against the pathogenic misfolded proteins involved in the disease. Hence, the hypothesis is that, if isolated and sequenced, these antibodies of human origin could potentially be used as therapeutic agents. This hypothesis was supported by evidence from the AN1792 active Aβ immunotherapy trial suggesting that AD patients with high serum titres of anti-Aβ antibodies that recognise amyloid plaques had slower rates of cognitive decline and disability as compared with patients with low titres [Hock 2002; Hock 2003].

In vivo characterisation of aducanumab was conducted in Tg2576 transgenic mice, which overexpress human APP and overproduce Aβ40 and Aβ42 and develop diffuse deposits and dense amyloid plaques in the brain in an age-dependent manner [Hsiao 1996].

Binding of aducanumab to amyloid plaques in vivo was demonstrated after single systemic administration of the antibody in Tg2576 mice and was evidenced by immunohistochemistry of brain sections from the dosed animals. This targeted engagement was shown to be dose-dependent, i.e., a correlation was established between the brain drug levels (measured biochemically) and the amount of antibody decorating the amyloid plaques (assessed by immunohistochemistry).

Efficacy of aducanumab was evaluated following chronic treatment of Tg2576 mice with chaducanumab (a murine chimeric version of aducanumab that retained the antigen-binding fragment variable regions and was used to reduce the risk of potential immunogenicity resulting from repeated dosing studies of a human antibody in mice). Treatment resulted in a statistically significant and dose-dependent reduction in brain amyloid burden (measured biochemically and histologically). The minimal effective dose of chaducanumab was 3 mg/kg. Plasma drug concentrations in both studies were consistent with the administered doses. The drug was detected in the brain at concentrations at or above the typical ~0.1% brain: plasma ratio expected for a systemically administered monoclonal antibody [Levites 2006; Wang 2018].

In vivo studies have described microglia-mediated phagocytosis as one of the mechanisms involved in immunotherapy-induced amyloid plaque clearance [Bard 2000]. This mechanism was assessed by comparing the efficacy of chaducanumab and of an aglycosylated variant with reduced Fc effector function in reducing amyloid burden in Tg2576 mice. A significant reduction of brain amyloid was observed upon treatment with chaducanumab, but not upon treatment with the aglycosylated version of the antibody. This result supported the hypothesis that recruitment of microglia and Fc-mediated phagocytosis of the amyloid plaques is a key component in the mechanism of action for aducanumab.

2.3. Quality aspects

2.3.1. Introduction

Aduhelm contains aducanumab as an active substance, a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody that specifically binds to soluble and insoluble aggregated forms of human amyloid beta (Aβ), which is key in the pathology of Alzheimer´s disease.

The finished product is presented as a concentrate for solution for infusion containing 100 mg/ml of aducanumab as the active substance.

Other ingredients are L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80 and water for injections.

The product is packaged in type I glass vial with halobutyl rubber stopper and a seal (aluminium) with a flip-off cap containing 170 mg or 300 mg aducanumab. Each vial contains a single dose of the finished product.

The packs contain 1, 2 and 3 vial(s). 1 vial pack contains 170 mg / 1.7 mL (red cap) or 300 mg / 3 mL (blue cap) concentrate. 2 vials pack contains 2 vials of 300 mg / 3 mL (blue cap) concentrate. 3 vials pack contains 1 vial of 170 mg / 1.7 mL (red cap) concentrate and 2 vials of 300 mg / 3 mL (blue cap) concentrate. Each vial is in an inner carton.

2.3.2. Active Substance

2.3.2.1. General information

The international non-proprietary name (INN) of the active substance is aducanumab. It is a monoclonal antibody that specifically binds to soluble and insoluble aggregated forms of human amyloid-beta (Aβ), which is key in the pathology of Alzheimer´s disease. The antibody is composed of complementarity-determining regions derived from human anti-amyloid beta monoclonal antibody framework regions and constant regions derived from human IgG1. Aducanumab has been developed as a disease-modifying treatment in adult patients with Alzheimer's disease.

Aducanumab is expressed in a Chinese hamster ovary (CHO) cell line, purified to a high degree of purity and formulated as a liquid.

Aducanumab is a recombinant human IgG1 monoclonal antibody that consists of two heavy and two kappa light chains connected by inter-chain disulfide bonds. The relative molecular mass of the molecule is 146 kDa (excluding any post-translational modifications).

Aducanumab is highly selective for human sequence aggregated amyloid-beta. Aducanumab removes aggregated forms of amyloid-beta via antibody-dependent cell-mediated phagocytosis (ADCP).

2.3.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The aducanumab active substance manufacturing process has been adequately described.

The active substance is manufactured using a recombinant CHO cell line. The cell culture process comprises three process steps: thaw of Working Cell Bank (WCB), inoculum/seed culture preparation and production bioreactor stage. The IPC testing strategy regarding the microbial contamination in the cell culture process is sufficiently described.

The production bioreactor volume is harvested by centrifugation. Subsequent purification utilises chromatography. Controlled parameters and in-process controls and tests were listed. The routine control strategy is sufficiently described.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. The origin of the nucleotide sequences coding for the variable region of the IgG heavy chain and the kappa or lambda light chain was described.

MCB, both WCBs, and EEPCB were tested for cell line identity and purity (microbial and adventitious agent contamination). Sufficient viability of MCB and both WCBs was demonstrated. Testing summary virology reports for the call banks were submitted. The range of used tests is considered sufficient, and results confirmed the identity to be Chinese hamster cells and that cell banks are free of bacteria, fungi, mycoplasma, and adventitious viruses. Preparation, qualification and storage of additionally prepared WCBs were described.

The Applicant provided a risk assessment of the process of raw materials to identify which raw materials are critical to ensure consistent process performance and product quality. For critical raw materials, attributes that are routinely tested were listed. The low-risk raw materials were also listed (compendial grade and non-compendial grade). The control tests for non-compendial raw materials with corresponding acceptance limits were provided.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the aducanumab active substance manufacturing process is given. The critical process controls were identified on the basis on the process and product knowledge, risk assessments, and experience with similar products and processes. The definitions, assessment and justification of criticality are presented in the dossier. Critical process controls were listed along with the control limits. Other controlled process parameters, in-process tests, and in-process controls have been identified not to impact product quality but may impact process consistency (e.g. yield, titer). These were also listed with their control limits.

There are no intermediates in the aducanumab active substance manufacturing process, but several sufficiently validated in-process holds.

Process validation

Validation of the active substance manufacturing process follows a 3-stage life cycle approach, including Process Design, Process Validation (PPQ), and Continued (Ongoing) Process Verification. Risk assessments and process characterisation and optimisation studies were used to determine the process parameter criticality and control limits.

The data from process validation batches demonstrate that all the steps of the active substance manufacturing process perform consistently. The control of the manufacturing process will be monitored as appropriate as part of product life cycle management via continued monitoring of critical quality attributes (CQAs) and critical controls and annual review of process performance through trending to ensure that product quality is maintained.

Re-processing of steps has been validated by using a scaled-down model. The available data confirmed that reprocessing has no negative impact on active substance quality. The Applicant claims 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. These protocols are submitted in the dossier.

Clearance of process-related impurities was studied. Where possible, validation was performed by using active substance batches from the full-scale manufacturing process. Submitted data for each monitored impurity confirm the consistent degree of clearance.

The column life-times as defined for the commercial manufacturing process, have been validated.

Hold time validation studies were performed to support the possible hold times defined for routine production. Summary of shipping validation for active substance was provided.

Manufacturing process development

The Applicant performed a risk assessment to determine the criticality of individual product attributes on the overall quality of the active substance and the finished product (CQA and non-CQA were defined). A risk-based approach is in compliance with ICH Q8 and ICH Q9. The evaluation of the risk of a given product attribute incorporated data from a variety of sources, such as structure-activity relationship (SAR) studies, nonclinical studies, clinical experience, compendial requirements, or general safety considerations. Relevant publications addressing the same attribute in similar molecules were also considered to provide further justification. Product CQAs were established using the product risk assessment methodology. The full rationale and methodology for the assessment of product risk and the identification of CQA were provided in sufficient detail and is considered acceptable.

Following identification of the product CQAs, process risk assessments were conducted on the active substance manufacturing process. Categorisation of controlled parameters is clearly described, and a

list of routinely performed testing and its criteria is provided. The process parameter criticality assessment is considered acceptable.

Selected process parameters were studied by using small-scale models. These studies are part of the development and were used to support the final process control strategy for the commercial manufacturing process. Small scale models used for development/validation studies, including their qualification, are described in sufficient detail.

The strategies for excursions from action limits and in-process specifications are outlined in the dossier and found acceptable.

The active substance has been manufactured using different scales and processes at multiple sites during development.

Characterisation

The aducanumab 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.

Aducanumab is a recombinant human IgG1 monoclonal antibody that binds to aggregated forms of human amyloid-beta (Aβ). Aducanumab was thoroughly characterized using a combination of analytical techniques evaluating the primary and higher-order structure, molecular heterogeneity, purity, post-translational modifications and potency. The proposed aducanumab mechanism of action concerns immunocomplex formation with aggregated amyloid-beta and subsequent elimination by Fc receptor-mediated phagocytosis (ADCP). It is also demonstrated that aducanumab binds to both soluble oligomers and non-soluble fibrils of aggregated Abeta peptide, as supported by the non-clinical data. As discussed by the applicant, aducanumab's target (Abeta) is non-cellular. Therefore, it does not promote cellular cytotoxicity mediated by Natural Killer cells or by complement and the membrane attack complex, both of which are distinguishing hallmarks of ADCC and CDC, respectively. To support this conclusion applicant discussed that in aducanumab development the clones that cross-reacted with full-length Amyloid Precursor Protein (APP) were excluded in order to avoid unintended cytotoxicity and the absence of cellular reactivity of aducanumab was further supported by additional non-clinical data demonstrating localization of aducanumab and no specific cytotoxicity. Overall, taking into consideration the totality of evidence-based on non-clinical data, the risk of Fc-mediated cytotoxicity is not anticipated, and hence the request to provide analytical characterization concerning ADCC or CDC bioassay could be waived.

The primary structure of aducanumab was studied by intact mass analysis of deglycosylated samples and peptide mapping analysis by HPLC with UV and MS detection after Lys-C or Asp-N treatment. The molecular mass of the intact molecules, HC and LC were consistent with theoretical values. Glycation or advanced glycation products were detected in some samples. Peptide mapping analysis provided visually comparable spectra to the reference standard, and full sequence coverage was confirmed by MS peptide analysis.

The secondary structure of disulfide linkages was characterized using Lys-C Peptide Mapping Under Non- Reducing Conditions. The higher-order structure was sufficiently evaluated by a combination of FTIR, Fluorescence spectroscopy, DSC, AUC and Hydrogen/Deuterium Exchange Mass Spectrometry. Provided results were comparable among tested batches and consistent with the reference standard. Biological activity of the aducanumab molecule was characterized.

Process and product-related impurities were identified and characterized appropriately. Results for clearance capacity for individual impurities were discussed in the dossier and found acceptable.

2.3.2.3. Specification

The specification was established in line with principles ICH Q6B. At the time of the CHMP opinion there was a minor unresolved quality issue outstanding, which does not have an impact on the benefit/risk ratio of the product. The current HCP method, qualified to be suitable for in-process testing, is considered acceptable as a release test for a short period of time and an update with the final method description and validation is requested.

Analytical methods

A brief description of non-compendial analytical methods, operating conditions and system suitability criteria were provided. For compendial methods, appropriate reference to a particular Ph. Eur. method was provided. Material, equipment, instruments and operation parameters were appropriately defined. Information provided on the description of analytical procedures is considered sufficient.

Pharmacopeial methods (endotoxin and bioburden) were assessed to ensure the ability to detect analytes in the presence of the active substance, and the provided results were acceptable. For every validated release and stability testing analytical method, a summary of validation results was provided. The analytical method validation strategy is deemed acceptable. Specificity confirmed the suitability of the intended purpose for individual methods. For quantitative assays, the linearity was demonstrated in sufficient range, and assay accuracy was validated for the respective linearity range. Precision parameters were appropriately determined, and the results were satisfactory. Methods precision parameters were comparable between individual QC testing sites. In addition, for impurity testing analytical procedures, the detection and qualification limits were reported.

In conclusion, the relevant method validation parameters were evaluated, and results conformed with predefined acceptance criteria. The validation is considered to be in line with the principles laid down in ICH Q2 (R1) guideline. Provided method validation summary is acceptable.

Batch analysis

Batch analysis data on 9 commercial scale of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

A two-tiered system of reference standards is used for commercial process. Primary reference standard (PRS) and working reference standard (WRS) are used. The PRS and WRS are placed on stability and tested per provided stability protocol. This protocol will be evaluated for updates when relevant changes to the active substance stability testing protocol occur.

Container closure system

The active substance is stored in single-use bioprocessing containers. The compatibility of the primary container closure and the DS is confirmed through stability studies presented in 3.2.S.7.1. together with container closure integrity and leachable/extractable studies.

2.3.2.4. Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is aducanumab 100 mg/ml concentrate for solution for infusion. The formulation buffer contains 16.2 mM L-histidine hydrochloride monohydrate, 3.8 mM L-histidine, 150 mM L-arginine hydrochloride, 10 mM L-methionine, 0.05% (w/v) polysorbate 80 and water for injection QS to final volume. There are no overages in the finished product formulation.

The product is intended for intravenous infusion. The product is supplied in a Type I glass vial closed with a stopper and seal with a flip-off cap. The information for finished product manufactured in seven different presentations differing in filling volume (170 mg, 300 mg, 450 mg, 600 mg, 750 mg, 850 mg and 1000 mg) was provided in quality dossier, however only two of them (170 mg and 300 mg) are the commercial presentations. The vials each contain a single dose of the finished product.

Solutions that can be used for its dilution prior to product's administration are not specified in this section, but it is clear from the other parts of the dossier (product information and Section P.2.6 Compatibility) that the required volume of Aduhelm is added to an intravenous (IV) bag containing 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

The manufacturing process development strategy was described in detail. The process control strategy was defined by using a standard stepwise approach based on process risk-assessment and individual characterization development studies. Categorization of input and output control criteria was clearly defined. A list of commercial process controls, including their criticality classification and proposed criteria, was provided. The rationale for criticality classification provided by the Applicant is accepted.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured by standard process covering dilution of the active substance, sterile filtration, aseptic filling, and visual inspection.

The process validation was performed based on pre-defined criteria. All parameters in the list of commercial process control provided in manufacturing development studies were included in the validation study, and therefore it is considered adequate.

Sterilisation parameters for product-contacting components are defined. Concerning the fact that the criteria follow the values recommended by the Ph. Eur. 5.1.1 and sterilization is performed at the GMP facilities; no additional information is required.

2.3.3.3. Product specification

The finished product specifications for release and self-life testing are found acceptable.

A risk assessment 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.

Product-related impurities are controlled as a part of finished product specifications. Release criteria are generally based on active substance acceptance limits. Justification of updated release and shelf-life criteria is endorsed.

Analytical methods

Compendial analytical methods are used for appearance, pH, osmolality, extractable volume, endotoxin and sterility. Suitability evaluation was done for endotoxin and sterility testing in line with relevant compendial requirements. Analytical methods are considered appropriately validated.

Batch analysis

Batch analysis data for representative commercial finished product lots are presented in the dossier. In summary, the submitted data confirmed consistent manufacture of the finished product material at proposed ranges of fill volume.

Reference materials

The reference standards used for testing the finished product are the same as those used to test the active substance (please refer to section Reference materials earlier in this report).

2.3.3.4. Stability of the product

All presented long-term stability data meet acceptance criteria and confirmed the stability of the finished product at the proposed storage conditions.

2.3.3.5. Adventitious agents

Animal or human-sourced materials used in cell line development and manufacture were listed.

The viral testing of the MCB, WCB and EoPC was performed in compliance with ICH Q5A (R1) at the appropriate levels. The cell banks complied with the predefined acceptance criteria and certificates of analysis were provided. This is acceptable. In general, the control strategy in the active substance manufacturing process in regard to microbial and adventitious agent safety seems appropriate.

2.3.3.6. GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological 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.

Major objections raised during evaluation (missing QP declaration and missing risk-assessment on the presence of nitrosamines) have been successfully resolved.

At the time of the CHMP opinion there was a minor unresolved quality issue outstanding, which does not have an impact on the benefit/risk ratio of the product. The current HCP method, qualified to be suitable for in-process testing, is considered acceptable as a release test for a short period of time and an update with the final method description and validation is requested.

Post-approval change management protocols were provided. Based on process validation protocols, it was agreed that the reprocessing by refiltration might be applied for commercial manufacture if required by the predefined circumstances without further notification to the regulatory agency. The proposed strategy introduced in Process Performance Qualification Protocol Overview for the Feed Forward Control using HIC Column Unit Operation is acceptable. Change Management Protocol for alternative Protein A Resin is sufficiently detailed.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. 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.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

Aducanumab shows high-affinity binding to immobilized amyloid β (Aβ) and truncated Aβ peptides, with the highest binding activity for the untruncated Aβ (EC50 0,34nM). Activity decreased slightly after truncating the peptide in positions 9, 12 or 16. However, truncations before residue 3-5 substantially reduced activity (EC50 = 12-36 nM). Further analysis identified the aducanumab binding epitope of Aβ isolated to residues 3-7.

Binding affinity data for aducanumab and ch12F6A (the chimeric murine analogue of aducanumab) showed that aducanumab and ch12F6A bind (fibrillar) aggregates, but not the soluble Aβ 1-40 and Aβ 1-42 monomers, with high affinity (resulting in EC50 = 0,1 nM and 0,2 nM, respectively).

This is also reflected in binding kinetics data. Aducanumab had a weak monovalent binding and fast dissociation rate to monomeric Aβ (KD = 9μM, kd >1/s). Increasing the valency of Aβ by presenting it as a dimer or tetramer increased the avidity of aducanumab (EC50 = 6,8 nM for the tetramer), further supporting that aducanumab binds more readily to Aβ fibrils and aggregates. Ex vivo, aducanumab or ch12F6A visibly bound to amyloid plaques in AD brain sections, but no further functional assessment was conducted in this experiment.

Human and nonhuman primate Aβ sequences are identical. The rodent Aβ sequence is similar to that of human and NHP Aβ, except for residues at positions 5, 10 and 13. Aducanumab bound to human Aβ42 with high (EC50=0,5 nM), and to murine Aβ42 with lower affinity (EC50 = 20nM), demonstrating that aducanumab is selective for human Aβ relative to the mouse peptide with a 40-fold difference in affinity.

To establish whether aducanumab can target amyloid plaques in the brain, ch12F6A was administered to approximately 70-week old Tg2576 transgenic mice. The Tg2576 model overexpresses a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671NL), which results in elevated levels of Aβ amyloid plaques. Tg2576 mice exhibit age-associated cognitive deficits. Approximately 1.3% of the

administered dose penetrated to brain tissue and showed binding to amyloid plaques. No increase in monomeric serum Aβ was observed, which correlates to the in vitro observations that aducanumab selectively binds aggregated Aβ.

The ability of aducanumab (ch12F6A) to reduce Aβ in the brain of 36-week old Tg2576 mice was evaluated in a 6-month repeat dose study, where a dose-response relationship was evaluated over a dose range of 0.3-1, 3, 10 or 30 mg/kg/week. Brain concentrations of aducanumab (ch12F6A) increased in a dose-proportional manner. A dose of 3 mg/kg/week was considered the minimal effective dose to reduce total Aβ levels in the brain and increasing doses proportionally improved total Aβ clearance.

In another 6-month study, the efficacy of aducanumab (ch12F6A and ch12F6A Agly, an antibody in which Fc effector function was reduced) and 3D6 (the murine monoclonal version of bapineuzumab) was evaluated in 40-week old Tg2576 mice, where animals received 3mg/kg per week of on of the antibodies investigated. At the end of the study, Aβ levels in the brain and Aβ plaque load in the cortex, hippocampus, and dentate gyrus was statistically significantly decreased in animals given ch12F6a. In contrast, no changes in Aβ load in the brain were observed in animals given ch12F6A Agly (see figures below). The lack of reduction in amyloid content in animals treated with this a-glycosylated variant suggests that Fc function is important in clearing aducanumab bound Aβ.

Figure 3: Concentration of Aβ1-40 and Aβ1-42 peptides in different brain extracts.

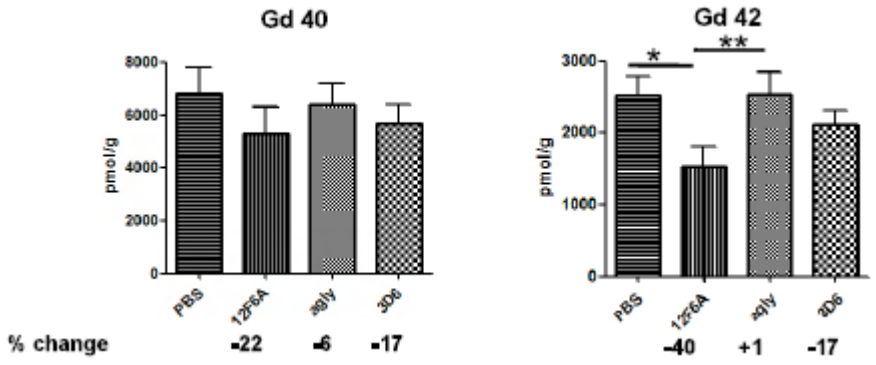
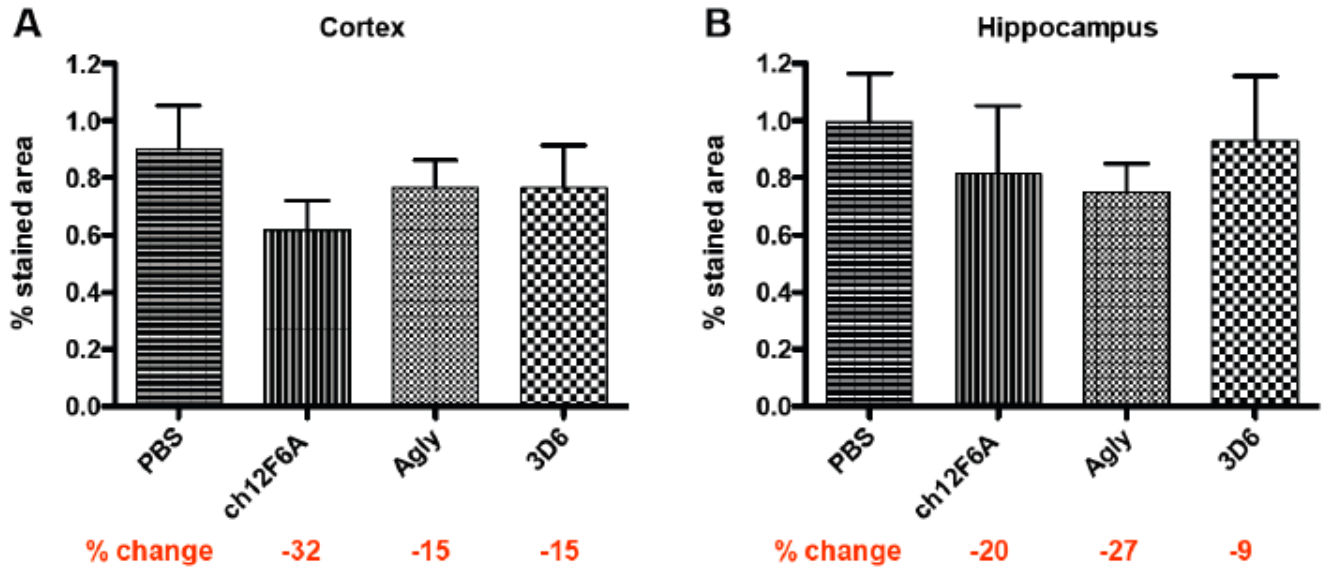
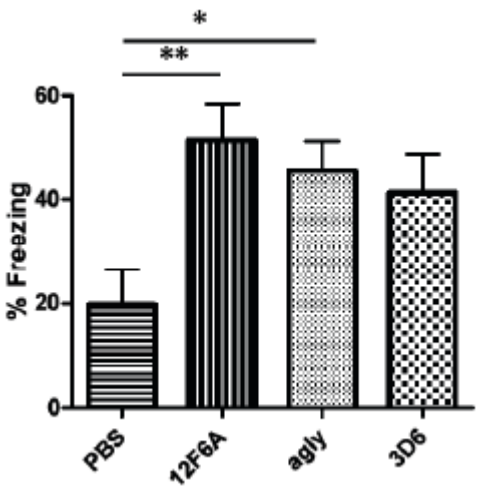


Figure 4: Quantification of Area Occupied by 6E10 Immunoreactive Amyloid Deposits.



Behavioural performance was evaluated in a contextual fear conditioning paradigm, where animals receiving aducanumab showed significantly greater memory performance (i.e. more freezing following appropriate fear conditioning) compared to animals given PBS. It should be noted that administration of ch12F6A Agly resulted in similar performance increases (see Figure below).

Figure 5: Freezing to context



The discordance between the amyloid content and the performance is noted. A possible explanation is that Ch12F6A Agly may have contributed to the clearance of soluble Aβ, resulting in the observed effects in mice. It is considered that while this study can be seen as supportive of the MoA, the capacity to provide meaningful data on PoC and translation to clinical efficacy is limited. Any evidence of efficacy and utilisation of aducanumab is therefore deferred to the clinical evidence.

Potential effects of aducanumab (ch12F6A) on Aβ level reductions and intraneuronal calcium homeostasis in aged (22-month old) Tg2576 mice was evaluated. While topical administration (0.4-1 mg/ml) of aducanumab resulted in anticipated reductions of Aβ plaque size after 3 weeks, long term systemic administration (10 mg/kg/week) did not lead to changes in plaque size, plaque number, plaque clearance rate, or overall amyloid burden relative to a control antibody. In this case, the difference in route of administration might be considered the driver of the observed results.

Calcium dysregulation is potentially a mediator of progressive neurotoxicity, and intracellular calcium concentration was elevated in Tg2576 mice at baseline compared to wild-type controls. However, administration of aducanumab restored normal calcium levels from week 2 onwards, and at the end of the 6-month treatment period, calcium levels were no longer elevated.

Fc effector functions were not evaluated because Aβ is a soluble protein. The Applicant considers that Aβ clearance is likely induced by aducanumab mediated ADCP in vivo. In vitro aducanumab has been demonstrated to induce ADCP. ADCC and CDC are not considered to be effector functions of aducanumab. An in vitro assay to demonstrate the absence of ADCC and CDC was requested in OC41, but these were not submitted. The Applicant did present data on the absence of ADCC and CDC in a TCR assay and in an ex vivo immunostaining PD-assay. Neither intended to specifically demonstrate absence of ADCC or CDC and are therefore considered supportive. The totality of evidence is sufficient to conclude that aducanumab is unlikely to induce ADCC or CDC.

Overall, the mode of action has been adequately demonstrated; aducanumab binds to amyloid-beta plaques, which are cleared via typical antibody clearance mechanisms. However, the AD animal models only partially recapitulate the pathology and phenotype in humans, and they should be considered of

limited predictive value. Hence, the proof of concept in vivo is limited, and the uncertainties can only be resolved clinically.

In line with ICH S6(R1), no dedicated safety pharmacology studies were conducted with aducanumab. This is acknowledged. The safety of aducanumab was evaluated in repeat-dose toxicity studies, which included relevant safety pharmacology endpoints. Repeat dose toxicity studies in cynomolgus monkey or Tg2576 mice did not reveal effects of aducanumab on the respiratory system, central nervous system, or cardiovascular system.

There are no drugs currently known to interact with the aducanumab target that could interfere with its pharmacodynamic effect; therefore, no nonclinical pharmacodynamic drug interaction studies have been performed.

2.4.3. Pharmacokinetics

The pharmacokinetics of aducanumab and of the murine, chimeric analogue of aducanumab (ch12F6A) has been investigated upon single-dose intravenous (IV), intraperitoneal (IP) and subcutaneous (SC) administration in aged Tg2576 transgenic mouse model. Multiple-dose toxicokinetics (TK) of the murine, chimeric analogue ch12F6A was examined in the Tg2576 transgenic mouse upon 13- and 26-week IV administration (10 – 500 mg/kg, QW).

In addition, multiple-dose toxicokinetics (TK) of aducanumab was examined upon weekly IV administration, which is the intended clinical route, in Cynomolgus monkey (4-wk) and Sprague Dawley rat (Embryo-Fetal Development and Fertility / Early Embryonic Development). SC multiple-dose toxicokinetics was examined in a monkey 4-wk tolerability and toxicology study.

2.4.3.1. Methods of analysis

Assays were developed for the evaluation of PK and immunogenicity in nonclinical studies. For the GLP studies in rats, monkey and mouse, assays were developed and validated according to guidelines, and sample analysis conducted in compliance with GLP. Aducanumab and ch12F6A were quantified using sandwich enzyme-linked immunosorbent assays (ELISA). The validation reports provided, which included (amongst others) the evaluation of precision and accuracy (intra- and inter-assay), specificity, selectivity, and sample stability (long-term, freeze-thaw), demonstrate that the assays were suitable for quantification of aducanumab in mouse plasma, monkey plasma and serum, and rat serum, whereas the assay for quantification of ch12F6A was suitable for detection in mouse plasma. ISR was shown to be acceptable for aducanumab in monkey plasma and serum analysis as well as ch12F6A in mouse plasma.

For detecting antibodies (ADAs) against aducanumab in mouse and monkey plasma, bridging ELISA immunoassays were developed. The anti-aducanumab ADA assays were selective, and the sensitivity was found to be 7.8 and 15.6 ng/mL for the assay in mouse and monkey plasma, respectively. Drug tolerance was 900 µg/mL of aducanumab in the presence of 500 ng/mL ADA in both mouse and monkey plasma. For detecting antibodies (ADAs) against ch12F6A in mouse plasma, a bridging ELISA immunoassay was developed. The anti-ch12F6A ADA assay was selective, and the sensitivity was found to be 15.6 ng/mL. Drug tolerance was 900 µg/mL of ch12F6A in the presence of 500 ng/mL ADAs.

2.4.3.2. Absorption

A single-dose study (non-GLP) in wild-type and Tg2576 mice receiving 2 mg/kg (wild-type and Tg2576) and 10 mg/kg (Tg2576 only) ch12F6A doses administered IV, SC and IP revealed similar exposure to ch12F6A for either route of administration, indicating 100% bioavailability for SC and IP dosing. In

Tg2576 mice, the exposure was linear over the dose range of 2 to 10 mg/kg. Half-life values ranged from ~90-95 hours in Tg2576 mice to 123 hours in wild-type mice.

Repeat-dose toxicokinetics studies (GLP) were performed in Tg2576 mice dosed with 10, 70 and 500 mg/kg of ch12F6A and 500 mg/kg aducanumab weekly via intravenous administration for 13 weeks and in mice dosed with 10, 40 and 250 mg/kg ch12F6A and 250 mg/kg aducanumab weekly via intravenous administration for 26 weeks. In both studies, exposure to ch12F6A and aducanumab were assessed after the first and last dose. In general, dose-proportional increases in exposure were detected, and accumulation ratios of ≤2.00 and ≤1.6 were observed over time for the first and second study, respectively, whereas aducanumab showed no accumulation in both studies. Also, no differences related to sex were observed, and the impact of ADA's was considered negligible for either ch12F6A or aducanumab.

Aducanumab was administered once weekly IV to male and female cynomolgus monkeys in a 4-week toxicology study, dosing 10 to 300 mg/kg (n=4-6) and in two separate 4-week studies dosing SC (QW, 250 mg/kg) or IV and SC (QW, 300 mg/kg) to male (n=3) cynomolgus monkeys. In general, aducanumab showed a biphasic decline, with an initial distribution phase, followed by a slow elimination phase. Upon IV weekly dosing, systemic exposure (AUC_{0-168}) of aducanumab increased in a dose-proportional manner over the dose range of 10 to 100 mg/kg and slightly less (-20%) than dose-proportional up to 300 mg/kg. No clear or consistent sex difference was observed on exposure. After 4-week IV multiple (QW) dosing, the volume of distribution was low, about 2–3 fold the plasma volume (i.e. 0.10 – 0.08 L/kg) in monkey, and in line with human (~0.14 L/kg). Plasma clearance in monkey was low (i.e. 1.06 - 0.86 ml/h/kg) and seems to be about 4-fold lower in humans (~0.23 ml/h/kg). Terminal elimination half-life ($T_{1/2}$) was approximately 66 h in monkeys and was ~25 days in human.
Upon subcutaneous administration to the monkey, absorption was relatively slow, having Tmax at 12 – 24 hrs after administration on the first day and upon 4-wk dosing (QW) and bioavailability (AUC_{0-168}) was 57% up to 75% following the last dose (300 mg/kg, QW). There was no evidence of ADA formation after 4-week IV aducanumab administration (10 to 300 mg/kg, QW). No unanticipated accumulation (about 1.5-fold after 4 weeks) or time-dependent changes in aducanumab exposure (AUC_{0-168}) following IV or SC repeat-dose administration was seen.

In a rat study focusing on early embryonic development, rats were dosed with 100, 300 and 1000 mg/kg aducanumab intravenously for a total of 9 (males) or 4-6 (females) weekly doses. Toxicokinetics analysis revealed that AUC_{last} increased relatively dose proportionally on both study days 0 and 49, with accumulation ratios ranging from 1.4 to 1.7 and no differences being observed between male and female rats.

2.4.3.3. Distribution

Formal tissue distribution and protein binding studies were not conducted with aducanumab. The low volume of distribution in cynomolgus monkeys ranging between 65 and 104 ml/kg suggests a distribution to the blood and the extravascular fluid within 2 to 5 times that of plasma volume (45 mL/kg). This is consistent with the known biodistribution of monoclonal antibodies.

In an embryo/fetal development study, female rats were dosed with two intravenous doses of 100, 300 and 1000 mg/kg aducanumab at gestation days 6 and 13, and aducanumab exposure was found in fetal serum at levels equal to or slightly lower than in maternal serum. No evidence for accumulation of aducanumab was observed when comparing GD6 and GD13 results.

Aducanumab transfer to maternal milk was not examined. However, as an IgG, aducanumab would be expected to be present in the first milk.

2.4.3.4. Metabolism

No metabolism studies with aducanumab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1).

2.4.3.5. Excretion

As aducanumab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size. Therefore, no specific studies to measure the excretion of aducanumab were conducted. The absence of excretion studies in accordance with ICH S6(R1).

2.4.3.6. Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolise via CYP P450 enzymes. In addition, the mechanism of action of aducanumab is not expected to have an effect on CYP450 enzymes or transporters.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Aducanumab toxicity after a single dose was not evaluated. This is acknowledged. No overt toxicity was observed after the first dose in repeat-dose toxicity studies with aducanumab in aged Tg2576 mice, cynomolgus monkeys, and Sprague Dawley rats.

2.4.4.2. Repeat dose toxicity

Repeat-dose toxicology studies have been conducted with aducanumab and ch12F6A in the pharmacologically relevant, aged Tg2576 mouse model (64 to 80 weeks of age at the start of dosing), which accumulates human amyloid in the brain in an age-dependent manner. A 4-week repeat-dose toxicology study was also conducted in the cynomolgus monkey to assess tolerability and off-target effects given the absence of Aβ in these young adult naïve animals.

Monkey studies

A 4-week repeat dose toxicity study in monkeys, which were given IV doses of aducanumab up to 300 mg/kg per week did not result in any aducanumab related findings. Given the absence of Aβ plaques, this is anticipated and demonstrates the typically absent off-target effects of therapeutic antibodies.

Mouse studies

The Applicant states that the 500mg/kg dose was selected as an MFD. It should be noted that ICH S6(R1) does not require such high doses for repeat dose toxicity testing unless the MFD approaches a 10x exposure multiple of the MRHD.

There was considerable (early) mortality in the 13-week study and required reassigning TK animals to the main study group. The Applicant states that mortality was comparable over all study groups. While this is acknowledged for early deaths, the total mortality is considerably higher in the treatment groups. Age-related sequelae leading to death is a reasonable justification for the mortality rates in the aducanumab treated groups and controls, which taken together with the dose and time-independent nature of both incidence rate and findings do not suggest an aducanumab related effect. However, the

main findings in the aducanumab animals were increased (micro) haemorrhage, and meningeal vascular inflammation, which was observed in animals given 70 mg/kg/week onwards and thrombosis in animals given 500 mg/kg/week ch12F6A. Microhaemorrhage, vascular inflammation and thrombosis have been associated with amyloid angiopathy. Because the incidence and severity were increased in animals receiving ch12F6A, this was considered test-article related. Meningeal vascular inflammation, acute microhaemorrhage, thrombosis and vascular thickening observed in chronic toxicity studies was fully reversible. It has been postulated that removal of vascular Aß deposits leading to vascular morphological abnormalities and transient increase in microhaemorrhage occur for antibodies targeting Aß deposits (e.g. bapineuzumab). Evidence for the recovery of vascular morphology was also described upon the continuation of the antibody treatment, suggesting a direct link between vascular amyloid clearance and vascular abnormalities. But clearance of cerebral amyloid angiopathy has not been observed for aducanumab. The Applicant considers that it is possible that increased clearance of the Aß could ultimately lead to vascular dysfunction and microhaemorrhage. A limitation in the possibility to elucidate the relationship between animal and human effects is the absence of mouse models of Amyloid-related imaging abnormalities (ARIA). With the exception of meningeal vascular inflammation, all findings resolved in the recovery period.

There were no other remarkable findings that could be considered attributable to ch12F6A. Except for microhaemorrhage in animals receiving 500 mg/kg/week aducanumab, there were no other remarkable findings. The NOAEL for ch12F6A was considered to be 10 mg/kg/week, (AUCtau: 10,200 µg*h/mL) in aged Tg2576 mice after 13 weeks of dosing).

Long term exposure to ch12F6A in aged (16-17 months) Tg2576 mice was evaluated in a 26-week repeat-dose toxicity study. Mortality in this study was comparable across all study groups, including controls. Early deaths were not considered to be treatment-related but rather due to age-related pathologies. Microscopic examination of these early-death mice showed similar incidence and severity of meningeal/cerebral vascular inflammation and vascular thickening to that found in the surviving animals. There were no changes in clinical observations, body weight, food consumption, ophthalmic examinations, clinical pathology parameters (haematology and serum chemistry), organ weights, and gross macroscopic findings with the administration of aducanumab 250 mg/kg weekly or ch12F6A up to 250 mg/kg weekly to mice. Meningeal vascular inflammation and vascular thickening were considered related to the disease model used; however, the incidence in animals receiving ch12F6A from 40 mg/kg/week onwards was slightly higher.

Mild subacute parenchymal necrosis with infiltration of gitter cells within the white matter of the frontal or parietal regions of the cerebral cortex was observed in 2 males receiving 10mg/kg/week ch12F6A. The finding was associated with vascular inflammation and thickening. This finding was also seen in the early death of an aducanumab 250 mg/kg/week male. The onset of the first two findings was considered to be in the recovery period. In the absence of correlating findings in control animals or a dose-response relationship, these findings were considered equivocal.

Microhaemorrhage observed in the 13-week study was also seen in the 26-week study, although the incidence and severity were comparable across all treatment groups. However, in 2 cases in the 250 mg/kg/week ch12F6 group, microhaemorrhage foci and area were larger than in other groups.

With the exception of evidence of haemorrhage (microscopic or acute), vascular inflammation, vascular thickening and thrombosis, there are no aducanumab related findings. These observations are already typical of amyloid pathology but could have been exacerbated by aducanumab administration.

2.4.4.3. Genotoxicity and carcinogenicity

Aducanumab is a protein derived from recombinant technologies and therefore is not expected to interact with DNA or other chromosomal material. In accordance with ICH S6 [ICH 2011], genotoxicity studies were not conducted. A weight of evidence approach suggests that aducanumab has a negligible carcinogenic risk.

2.4.4.4. Reproductive toxicity

A complete segment I-III evaluation of reproductive toxicity of aducanumab was performed in rats, with once-weekly IV dosing of up to 1000 mg/kg aducanumab.

In the fertility study, males were administered aducanumab 4 weeks prior to mating for a total of 9 doses. Females received aducanumab for 2 weeks prior to mating and until GD 7 for a total of 4-6 doses. Transient single cases of rales were noted in animals receiving 300 mg/kg/wk aducanumab and above with a dose-dependent incidence. These findings were not adverse due to the single occurrence and transient nature of the finding. There were no other notable clinical observations. There was no change in body weight gain or food consumption or clinical pathology, oestrous cycles, reproductive parameters (mating, fertility, copulation, and conception indices), spermatogenesis, gross examinations, organ weights, and laparohysterectomy parameters (corpora lutea, implantations sites, number and location of embryos, and early resorptions). The NOAEL was the highest dose tested, 1000 mg/kg/week (AUCtau 490,000 µg*h/mL). Aducanumab had no adverse effect on fertility and early embryonic development in rats. In the embryofoetal development study, pregnant rats were given up to 1000 mg/kg aducanumab via IV administration per week from GD6 and GD13. There were no aducanumab-related clinical observations at the daily examinations, post dose observations, and no effects on mean maternal body weight gains, body weights, food consumption, net body weights, net body weight gains, gravid uterine weights, and macroscopic findings at any dose of aducanumab. There were no effects on intrauterine growth, and survival and foetal morphology (external, visceral, and skeletal) were unaffected by test article administration at any dose of aducanumab.

In conclusion, based on the lack of effects, the aducanumab dose of 1000 mg/kg weekly (Cmax: 18,700 µg/mL, AUCtau: 274,000 µg*h/mL) was considered the NOAEL for maternal and EFD toxicity in rats. However, it should be noted that the placental transfer of therapeutic antibodies in rats is not fully comparable to humans due to physiological differences. Studies in juvenile animals have not been conducted with aducanumab. Given that the target indication of Alzheimer's disease does not include young patients, this is acceptable.

2.4.4.5. Local tolerance and other studies

Based on repeat dose toxicity studies, aducanumab is not expected to cause issues with local tolerance. Aducanumab staining was observed in human, Tg2576 mouse and cynomolgus cerebrocortical plaques (mouse), blood vessel wall (mouse and human) and cytoplasmic staining of mesenchymal cell cytoplasm in various tissue (human and cynomolgus monkeys). Most of the staining in human and monkey tissue was only observed at 0.5 µg/ml, the highest concentration tested or was considered rare or equivocal. In mouse, staining was primarily directed to amyloid plaques and blood vessel wall, consistent with amyloid pathology. It is anticipated this is will also be relevant for the human AD population. Aducanumab is hemocompatible. Toxicology antigenicity studies were not conducted for aducanumab. Repeat dose toxicity studies in Tg2576 mice and cynomolgus monkeys did not suggest that aducanumab adversely affected the immune system. The absence of dedicated immunotoxicity studies has been appropriately justified. No toxicity studies were done regarding impurities for aducanumab.

2.4.5. Ecotoxicity/environmental risk assessment

As a recombinant protein, aducanumab is not anticipated to pose a risk to the environment. Further evaluation of environmental risk is not needed, in line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 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, aducanumab is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

The ability of aducanumab (ch12F6A) to reduce Aβ in the brain and thereby improve cognitive performance was evaluated in aged (9-10 month-old) and very old (18-month-old) Tg2576 mice with ch12F6A and with an aglycosylated variant in the younger mice.

At the end of the study, Aβ levels in the brain and Aβ plaque load in the cortex, hippocampus, and dentate gyrus was statistically significantly decreased in younger animals given ch12F6a. In contrast, no changes in Aβ load in the brain were observed in animals given ch12F6A Agly. Behavioural performance was evaluated in a contextual fear conditioning paradigm, where animals receiving aducanumab showed significantly greater memory performance compared to animals given PBS. It should be noted that administration of ch12F6A Agly resulted in similar performance increases. Ch12F6A Agly may have contributed to the clearance of soluble Aβ, resulting in the observed effects in mice.

Furthermore, long term systemic administration to very old mice did not lead to changes in plaque size, plaque number, plaque clearance rate, or overall amyloid burden relative to a control antibody. The Applicant considers that this is consistent with non-clinical studies previously published, and might be related to the characteristics of the mouse models where amyloid production outweighs the clearance mechanisms induced by the treatment.

Overall, it is considered that mouse models of amyloid deposition, as used in the studies, have a limited ability to concomitantly recapitulate all the hallmarks of AD pathogenesis. The study is therefore considered as supportive of the MoA but not of a PoC for the treatment of patients in any particular age group. The data do not conclusively suggest that aducanumab can modify the AD disease state as a proof of concept.

Three animal species have been used to study the pharmacokinetics of aducanumab in pre-clinical testing: mouse, rat and monkey. In mouse, relatively dose-proportional increases in exposure to ch12F6A were observed, with no differences between sexes. There was limited evidence for accumulation of ch12F6A after repeated dosing, with ARs ≤2.0 for all studies. The elimination half-life $t_{1/2}$ observed in a single-dose study with ch12F6A was 90-123 hours. Mice dosed with aducanumab showed no evidence of accumulation over time, with no significant ADA formation (detected in ~10 % of cases).

Monkeys dosed with aducanumab showed limited accumulation over time (AR ≤1.5), also without significant ADA formation and no differences between sexes. The monkey studies revealed an elimination $t_{1/2}$ of ~66 hours, whereas the $t_{1/2}$ in humans was ~25 days. Rats dosed with aducanumab showed limited accumulation (AR ≤1.7), similar to AR values obtained in mice dosed with ch12F6A.

The findings from toxicology studies included microhaemorrhage, vascular inflammation and thrombosis, which are known to be associated with amyloid angiopathy. Because the incidence and severity were increased in animals receiving ch12F6A, this was considered test-article related. Meningeal vascular inflammation, acute microhaemorrhage, thrombosis, and vascular thickening observed in chronic toxicity studies were fully reversible. It has been postulated that removal of vascular Aß deposits leading to vascular morphological abnormalities and transient increase in microhaemorrhage occur for antibodies targeting Aß deposits (e.g. bapineuzumab). Evidence for the recovery of vascular morphology was also

described upon the continuation of the antibody treatment, suggesting a direct link between vascular amyloid clearance and vascular abnormalities. But clearance of cerebral amyloid angiopathy has not been observed for aducanumab. The Applicant considers that it is possible that increased clearance of the Aß could ultimately lead to vascular dysfunction and microhaemorrhage. The relationship between animal and human effects cannot be conclusively elucidated due to the absence of mouse models of ARIA.

2.4.7. Conclusion on the non-clinical aspects

The efficacy and safety have been adequately discussed from a non-clinical perspective, to the limited extent to which these can be demonstrated from such perspective.

2.5. Clinical aspects

2.5.1. 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**

Clinical Study (Status)	Study Design and Objectives	Aducanumab Dose Regimen	Number of Participants Treated
Studies in Participants with Alzheimer's disease			
221AD101: CSR 221AD101 (completed)	Phase 1, multicentre, randomised, double-blind, placebo-controlled, single ascending dose, dose escalation, sequential cohort study to determine safety, tolerability, and PK of aducanumab in participants with mild to moderate Alzheimer's disease	Single dose: 0.3, 1, 3, 10, 20, 30, or 60 mg/kg IV	Placebo: 14 Aducanumab: 39
221AD103: CSR 221AD103 Close-out (placebo-controlled period: completed; LTE period: terminated)	Phase 1b, multicentre, randomised, double-blind, placebo-controlled, multiple-dose, dose escalation, staggered parallel-group study to assess the safety, tolerability, PK, and PD of aducanumab in participants with prodromal or mild Alzheimer's disease with positive Aβ PET scan.[1] The study includes a 54-week placebo-controlled period followed by a dose-blind LTE period of up to 8 years in duration.	Q4W: 1, 3, 6, 10 mg/kg IV, titration from 3 to 6 mg/kg over 8 weeks (ApoE ε4 carriers and noncarriers)[2] or titration from 1 to 10 mg/kg over 44 weeks (ApoE ε4 carriers only)[3]	196 participants (aducanumab and/or placebo) Placebo-controlled Period Placebo: 48 Aducanumab: 148 LTE Period Aducanumab: 143 (37 participants switched from placebo to aducanumab in LTE, termed "late starters")

Clinical Study (Status)	Study Design and Objectives	Aducanumab Dose Regimen	Number of Participants Treated
Studies in Participants with Alzheimer's disease			
221AD104: CSR 221AD104 (completed)	Phase 1, multicentre, randomised, double-blind, placebo-controlled single- and multiple-ascending-dose study to evaluate the safety, tolerability, PK, and immunogenicity of aducanumab in Japanese participants with mild to moderate Alzheimer's disease	Cohorts 1 & 2: Single dose of 1 or 3 mg/kg IV, followed 8 weeks later by doses of 1 or 3 mg/kg Q4W Cohorts 3 & 4: titration from 1 to 6 mg/k[4] IV (ApoE ε4 carriers) or titration to from 1 to 10 mg/kg[4] IV (ApoE ε4 noncarriers)	Placebo: 4 Aducanumab: 17
221AD205: Synopsis CSR 221AD205 (terminated)	Phase 2, multicentre, randomised, double-blind, parallel-group, controlled multiple-dose study in participants with MCI due to Alzheimer's disease or mild AD dementia to evaluate the safety of continued dosing in participants with asymptomatic ARIA, followed by an LTE period (Participants randomised [1:1] to 1 of 2 groups that differ as to whether action is taken with aducanumab in the setting of asymptomatic moderate or severe ARIA on MRI.)	Q4W: titration from 1 to 10 mg/kg IV (ApoE ε4 carriers and noncarriers)	Aducanumab: 52 500 participants planned
221AD301: CSR 221AD301 (placebo-controlled period: completed; LTE period: terminated)	Phase 3, multicentre, randomised, double-blind, placebo-controlled, multiple-dose, parallel-group study to evaluate the efficacy and safety of aducanumab in participants with early Alzheimer's disease[5], followed by a dose-blind LTE period	Q4W: Low dose for ApoE ε4 carriers (3 mg/kg IV after an initial 8-week titration period[6]). Low dose for ApoE ε4 noncarriers (6 mg/kg IV after an initial 24-week titration period[7]). High dose for ApoE ε4 carriers and noncarriers (10 mg/kg IV after an initial 24-week titration period[4].	1647 participants (aducanumab or placebo) (Participants who were on placebo and switched to aducanumab during the LTE period are referred to as "late starters.")

Clinical Study (Status)	Study Design and Objectives	Aducanumab Dose Regimen	Number of Participants Treated
Studies in Participants with Alzheimer's disease			
221AD302: CSR 221AD302 (placebo-controlled period: completed; LTE period: terminated)	Phase 3, multicentre, randomised, double-blind, placebo-controlled, multiple-dose, parallel-group study to evaluate the efficacy and safety of aducanumab in participants with early Alzheimer's disease[5], followed by a dose-blind LTE period	Q4W: Low dose for ApoE ε4 carriers (3 mg/kg IV after an initial 8-week titration period[6]). Low dose for ApoE ε4 noncarriers (6 mg/kg IV after an initial 24-week titration period[7]). High dose for ApoE ε4 carriers and noncarriers (10 mg/kg IV after an initial 24 week titration period[4].	1638 participants (aducanumab or placebo) (Participants who were on placebo and switched to aducanumab during the LTE period are referred to as "late starters.")
Study in Healthy Participants			
221AD102: CSR 221HV102 (completed)	Phase 1, multicentre, randomised, open-label, parallel-arm bioavailability study in healthy participants	Single dose: 6 mg/kg IV or 420 mg SC	Aducanumab IV: 14 Aducanumab SC: 14

Aβ = β-amyloid (peptide derived from membrane bound amyloid precursor protein); AD = Alzheimer's disease; ApoE ε4 = apolipoprotein E ε4; ARIA = amyloid-related imaging abnormality; EOT = end of treatment; ET = early termination; IV = intravenous; LTE = long-term extension; MRI = magnetic resonance imaging; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; Q4W = every 4 weeks; SC = subcutaneous.

[1] This study included participants with prodromal Alzheimer's disease (International Working Group nomenclature) or mild Alzheimer's disease (National Institute on Aging and the Alzheimer's Association nomenclature). This study population for Study 221AD103 will be described as participants with MCI due to Alzheimer's disease and mild AD dementia in this summary.

[2] Titration sequence of 3, 3, and then 6 mg/kg thereafter.

[3] Titration sequence of 1, 1, 3, 3, 3, 3, 6, 6, 6, 6, 6, and then 10 mg/kg thereafter (ApoE ε4 carriers only).

[4] Titration sequence of 1, 1, 3, 3, 3, 3, and then 6 mg/kg thereafter.

[5] This study population will be described as participants with MCI due to Alzheimer's disease and mild AD dementia in this Summary.

[6] Titration sequence of 1, 1, and then 3 mg/kg thereafter.

[7] Titration sequence of 1, 1, 3, 3, 6, 6, and then 10 mg/kg thereafter.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Aduhelm 100 mg/ml concentrate for infusion solution is indicated as a disease-modifying treatment in adult patients with Alzheimer's disease. The proposed posology is an intravenous (i.v.) infusion over approximately 1 hour every 4 weeks. Dose titration is required with a starting dose of 1 mg/kg for the first two infusions. This is increased to 3 mg/kg for the third and fourth infusions, to 6 mg/kg for the fifth and sixth infusions, followed by 10 mg/kg every 4 weeks.

The pharmacokinetics of aducanumab was evaluated in healthy volunteers (study 221HV102) and in patients with Alzheimer's disease (studies 221AD101, - 103, -104, -205, -301 and -302). Intensive blood sampling was only applied in studies 221HV102 (see section 2.1.3 for pharmacokinetic results), 221AD101 (see section 2.1.6 for pharmacokinetic results) and 221AD104. In the other studies, sparse sampling was applied to be included in the popPK analysis. Due to early study termination, no results were obtained from study 221AD205.

2.5.2.1.1. Analytical methods

Aducanumab was analysed in human serum using an enzyme-linked immunosorbent assay (ELISA). Different batches of critical reagents have been used, and the appropriateness of these batches was questioned. It appeared that all lots of critical reagents used in the serum aducanumab drug concentration assay were adequate qualified for use by partial validation. On request, the certificate of analysis used in studies 221AD101, - 102, and -104 were submitted. The ELISA method applied in the early studies 221AD101 and 221AD103 with a LLOQ of 0.2 µg/ml showed that accuracy was not always within normal criteria for ELISA methods. The method was partially validated by applying a higher LLOQ (0.6 µg/ml). Evaluation of parallelism has not been carried out. In response, the applicant argued that no parallelism issues are expected due to the use of aducanumab specific neutralising anti-idiotypic mAb capture antibody and lack of interferences by relevant molecules. Although an effect cannot be fully ruled out, this issue was not further pursued. Intra- and inter-assay accuracy and precision were within the normal acceptance criteria for ELISA. Stability has been proven over the study sampling handling. During the study sample analysis run performance was within accepted criteria. Incurred sample reanalysis showed that the analyses were reproducible.

Aducanumab CSF levels were determined using validated methods. The concern regarding the use of different batches of critical reagents and the lack of parallelism data has been addressed in line with the concern raised for serum analysis. The ELISA method applied in the Phase 1b study 221AD103 was subject to some inaccuracy; however, the ELISA method used in the main Phase 3 studies 221AD301 and 221AD302 showed acceptable accuracy. Stability has been proven over the study sampling handling; however, frozen -70°C long-term stability to cover the age of the samples up to 1541 days is ongoing. Twelve-month stability data has been provided up to now. It is estimated that stability data covering 1541 days will be available in Q3 2024.

For the quantitative analysis of the t-tau, p-tau, Aβ 1-40, and Aβ 1-42 biomarkers in CSF, commercially available immunoassay kits were applied. The assays were partly validated. In addition, the performance of the assays was based upon manufacturers claims and based upon these claims, performance could be considered acceptable regarding selectivity/specificity, accuracy, precision and stability.

In principle, commercial assays should be revalidated by the applicant to confirm the assays' performance parameters. As the results were used for exploratory endpoints, this issue is not further pursued.

The assessment of ApoE alleles to identify ApoE ε4 carriers and non-carriers was performed by using commercially available kits. The analytical performance of the assay was revalidated.

Detection of anti-aducanumab antibodies was performed using a tiered approach involving screening, confirmatory, and titre assays. Due to the very low incidence of ADA-positive individuals, further direct measurement of neutralising antibodies to aducanumab was not assessed. Instead, the neutralising activity of anti-aducanumab antibodies was evaluated by integrating anti-aducanumab antibody results with aducanumab exposure data to inform on the presence and clinical impact of neutralising antibody activity.

The pop-PK model (a two-compartment model with intravenous (iv) infusion and first-order elimination with linear clearance) for the description of the aducanumab pharmacokinetics is considered to be developed adequately. Pharmacokinetics of aducanumab administered at doses of 0.3 – 60 mg/kg were well described using this model. The performance of the final PK model was acceptable. The results of the non-parametric bootstrap showed that the median of the bootstrap parameters is in line with the population estimates. Graphical evaluations of the final model suggested adequate performance. For a more robust evaluation of the performance of the model, it has been requested to submit a separate pcVPC plot for each Phase 3 study and pcVPCs from the multiple-dose part of the Phase 1 studies and to submit plots of the effect of covariates (baseline weight, sex, age, race, MMSEBL) on the steady-state exposure. It appeared that the pcVPCs seemed adequate, showing that the popPK model can well describe the aducanumab concentrations in the multiple-dose Phase 1 and Phase 3 studies. Furthermore, the effect of covariates (baseline weight, sex, age, race, MMSEBL) on the steady-state exposure is considered not clinically relevant. The popPK analysis showed no significant effect of ADAs on aducanumab clearance. Consequently, the systemic exposure of aducanumab was not affected by ADA positive individuals. The NONMEM input and output files for this analysis were submitted on request.

2.5.2.1.2. Bioavailability/bioequivalence

The bioavailability of aducanumab is 100% per definition since it is administered as an i.v. infusion. For a possible future application, the pharmacokinetics after s.c. administration was evaluated, indicating an absolute bioavailability of 54%.

Three manufacturing processes were used to produce aducanumab for clinical studies. Extensive physiochemical, biochemical, and in vitro biological comparability of the drug substance and drug product processes manufactured to date were carried out. No bioequivalence studies are considered needed since it is an aqueous solution administered via i.v. infusion. With regard to the drug substance and mannose content, reference is made to the quality assessment.

After i.v. administration, no deviation from dose proportionality was apparent up to a dose of 60 mg/kg. Aducanumab is proposed to be given at a dose of 1 to 10 mg/kg. Based upon single-dose data, inter-subject variability in Cmax, AUC, and clearance is about 20 – 25%.

Based upon popPK analysis, steady-state at a 10 mg/kg Q4W dosing regimen is expected to be achieved after 4 months. Considering the recommended titration scheme, this would imply that a steady-state would be achieved after about 10 months. No unexpected accumulation (1.7-fold) is observed.

Titration to the target dose was implemented in all regimens to reduce the incidence of ARIA, especially in ApoE ε4 carriers. At the same dose level, aducanumab levels were generally similar in both ApoE ε4 carriers and non-carriers. No differences in pharmacokinetic characteristics were detected between the pivotal studies 221AD301 and 221AD302 when comparing the post-hoc pharmacokinetic parameters. However, changes to dose and management of ARIA-E impacted the duration a subject spends on steady-state, thereby potentially affecting pharmacology.

PopPK analysis showed pharmacokinetics typical for an IgG1 mAb drug and characterised by a low central (3.59 l) and peripheral volume distribution (6.04 l), a low clearance (0.0159 l/h), and a long elimination half-life of 24.8 days. Furthermore, the model indicated linear clearance, no long-term drift in clearance at the doses of interest and no target mediated kinetics.

The estimated steady-state exposure of $AUC_{tau(0\text{-}4weeks)}$) from the pop-PK model were 11500 µg.h/ml at the 3 mg/kg dose, 22900 µg.h/ml at the 6 mg/kg dose and 36400 µg.h/ml at the 10 mg.kg dose.

2.5.2.1.3. Distribution

Aducanumab being an IgG1-class antibody protein, is not expected to bind to plasma proteins. Limited data indicated that aducanumab is distributed to CSF and that aducanumab may reach measurable concentrations in the brain. Due to their high molecular weight and low lipophilicity, mAbs such as aducanumab are largely confined to the vascular and interstitial spaces and, hence, have a small volume of distribution somewhat larger than the blood compartment volume. This is confirmed by the popPK estimated central volume of distribution of aducanumab being 3.57 l, and the peripheral volume of distribution being 6.04 l.

2.5.2.1.4. Elimination and metabolism

Excretion of aducanumab in urine and faeces has not been studied. The popPK estimated terminal elimination half-life was approximately 25 days and clearance approximately 0.0159 l/h, indicating that aducanumab is a low clearance drug.

No metabolism studies were conducted. Given that aducanumab is an IgG1-class antibody protein, it is expected to be degraded by enzymatic proteolysis into small peptides and amino acids.

2.5.2.1.5. Special patient populations

No dedicated clinical studies were conducted in special populations, including subjects with renal or hepatic impairment. The effect of various intrinsic and extrinsic factors on the pharmacokinetics of aducanumab (baseline weight, age, MMSEBL (Mini-Mental State Examination), sex, and race) were assessed in pop-PK analysis.

Aducanumab is an antibody with a molecular mass of 146 kDa and is therefore not expected to be excreted in the urine. Therefore, formal studies in patients with renal impairment to study the effect of renal function are considered not necessary.

No direct effect of hepatic function on the pharmacokinetics of aducanumab is expected because antibodies are principally cleared by catabolism. Therefore, formal studies in patients with hepatic impairment to study the effect of hepatic function are considered not necessary.

Gender, race (Caucasian + other categories vs Asians), weight (range 35.6 – 162 kg), age (50 – 91 years) and MMSE (mini-mental state examination; score 14 – 30) were identified as a statistically significant covariate on aducanumab CL and/or Vd based on pop-PK analysis; however, the relative change from reference was within the 80 – 125% criteria and thus not considered clinically relevant.

With regard to the elderly, on request, the applicant provided a detailed summary of included subjects sorted by age category. The majority of patients/subjects included were elderly (2225/2961 patients/subjects). The majority of elderly subjects were between 65 – 74 years.

The observed in-study False Positive Rate (FPR) for the first in human single ascending dose phase 1 study 221AD101 was 8%. In addition, 4 participants were ADA positive at baseline, out of a total of 53 total enrolled.

For the study 221AD103 and pivotal 221AD301 and 221AD302 studies, the anti-drug antibody assay was modified and revalidated. For each study, in-study baseline samples were used to determine the screening and confirmatory cut points for the various lots of labelled drug used during sample analysis and served to better characterise the treatment-naïve study population. Study 221AD103 had an observed FPR of 1% (2/194). The FPR for 221AD301 was 0.6% (10/1616). Study 221AD302 had an FPR of 1.2% (19/1604).

2.5.2.1.6. Drug-drug interactions

Given that aducanumab is an IgG1-class antibody protein, it is expected to be catabolised into amino acids by the general protein degradation process and is unlikely to affect the metabolic enzymes of low-molecular-weight drugs. Metabolic enzymes, transporters, and protein binding, factors generally involved in interactions with low-molecular-weight drugs, are not considered to play a role in the pharmacokinetics of aducanumab. In addition, low-molecular-weight drugs are unlikely to affect the pharmacokinetics of aducanumab. Therefore, no in vitro or in vivo drug-drug interaction studies were conducted, which is considered acceptable. As the proposed statement in the SmPC that "aducanumab does not appear to be a cytokine or cytokine modulator" could not be justified, the applicant had accepted to delete it.

2.5.2.2. Pharmacodynamics

2.5.2.2.1. Mode of action

Aducanumab is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) targeting aggregated forms of amyloid-beta in the brain such as soluble oligomers and insoluble fibrils. Upon systemic administration, aducanumab enters the brain and clears amyloid-beta plaques through a microglia-mediated phagocytosis mechanism. Non-clinical pharmacology studies in Tg2576 transgenic mice showed binding of aducanumab to amyloid plaques after systemic administration, and that the target engagement was dose-dependent. Efficacy of aducanumab as chronic treatment was evaluated in the same mouse model, demonstrating a dose-dependent effect involving the recruitment of microglia around the amyloid plaques and a phagocytosis-mediated clearance of the plaques.

2.5.2.2.2. Primary pharmacology

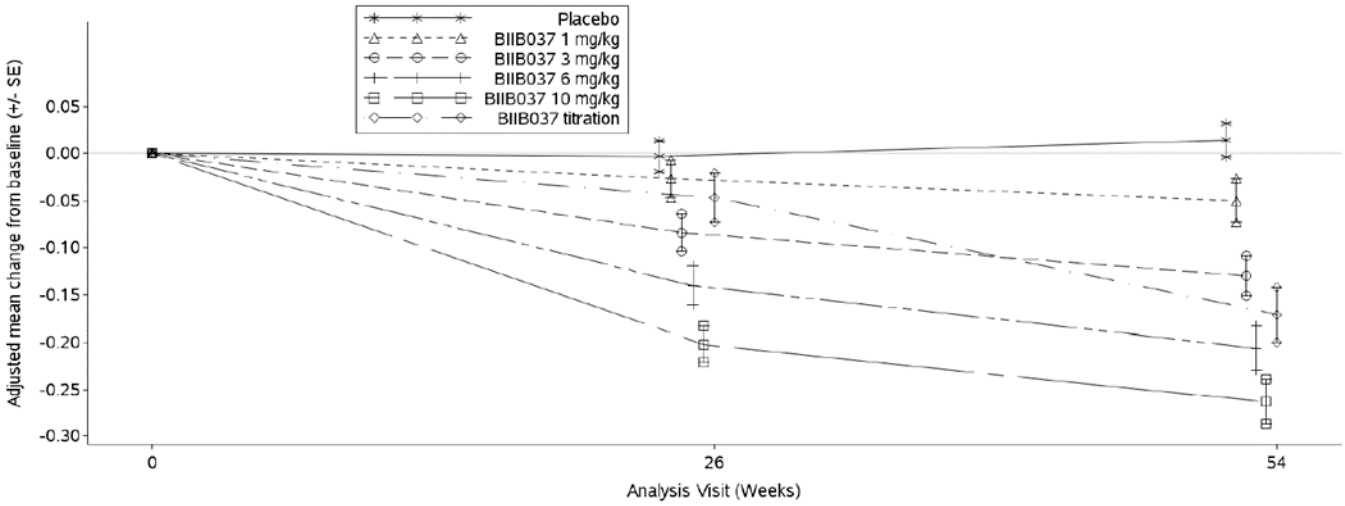
In Studies 103, 301 and 302, the effect of aducanumab on cerebral amyloid load was evaluated. PET scans of the brain were performed to measure brain Aβ plaque levels, which were quantified as a composite standard uptake value ratio (SUVR). All studies included patients with MCI due to AD or mild AD with confirmed cerebral Aβ pathology. The effect of aducanumab on the cerebral amyloid plaque load was the secondary objective of Study 103. In the Phase III Studies 301 and 302, a subsample of the patients was included in a PET sub-study.

SUVR is an established quantitative measure of Aβ PET images. In the case of Aβ PET imaging, SUVR serves as an estimate of brain Aβ levels. A composite SUVR was calculated for a composite of brain regions comprising frontal, parietal, lateral temporal, sensorimotor, anterior, posterior cingulate, and occipital cortices with the whole cerebellum as a reference region.

Although not clearly described, based on the Applicant's references, it is assumed that the mean florbetapir uptake was extracted from gray matter within the specified brain regions relative to uptake in the whole cerebellum (white and gray matter). This summary measure was used as the florbetapir cortical mean for each subject. A SUVR threshold of 1.10 was used to classify amyloid-negative from amyloid-positive subjects (Landau et al, 2012). In literature, centiloid cut-offs for PET imaging are described within a range that optimally discriminates negative from positive visual reads between 25 and 35 CL (Rowe et al, 2018).

In Study 103, treatment with aducanumab lowered the levels of amyloid load in a dose-dependent way compared to placebo, see Figure 6 below. The 10 mg/kg titration dose falls between the 3 mg/kg and 6 mg/kg dose in the first 54 weeks of treatment. This is not unexpected since the 10 mg/kg dose was titrated over 44 weeks. As reflected in the figure, the reduction in cerebral amyloid load seems to be dose-dependent.

Figure 6: Line Plot of Aβ PET Composite SUVR (Reference Region = Cerebellum) Adjusted Mean Change From Baseline (±SE) Over Time by ANCOVA in Arms 1-9: Placebo-Controlled Period (Study 103)

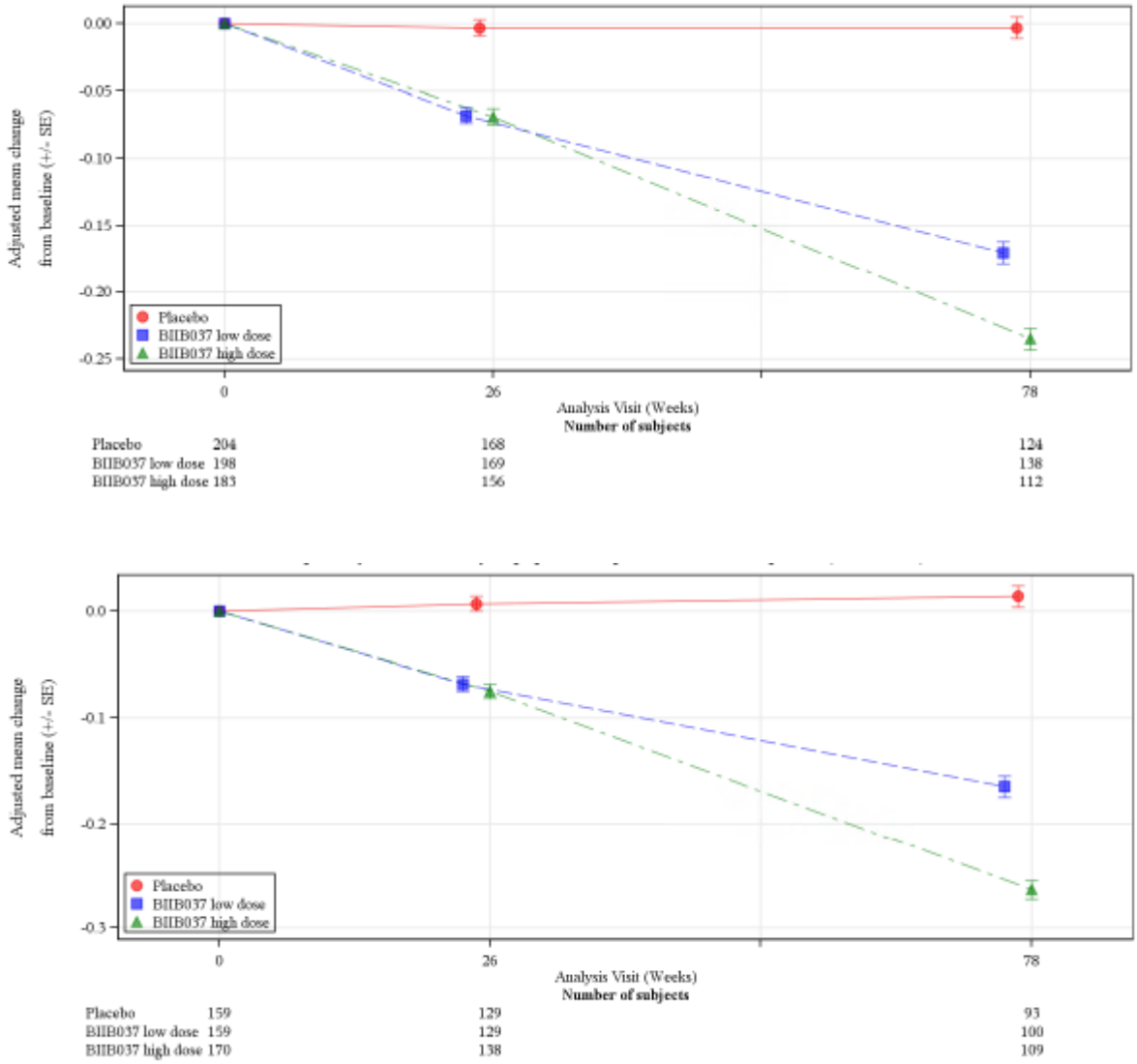


		Number of subjects	
Placebo	42	42	38
BIIB037 1 mg/kg	26	26	21
BIIB037 3 mg/kg	29	27	26
BIIB037 6 mg/kg	24	23	23
BIIB037 10 mg/kg	28	27	21
BIIB037 titration	18	17	16

NOTE: Adjusted means for each treatment group and standard errors were based on an ANCOVA model at each timepoint. An ANCOVA model was fitted with change from baseline as dependent variable, and with treatment group, baseline value and laboratory ApoE status(carrier and non-carrier) as independent variables.
Abbreviations: SE = standard error.

Results in line with the above are reported from the PET substudies of Studies 301 (Figure 7, upper panel) and 302 (Figure 7, lower panel).

Figure 7: Line Plot of Adjusted Mean Change From Baseline in Amyloid PET Composite SUVR (Reference Region = Cerebellum) Over Time by MMRM – 18F-Florbetapir Amyloid PET Analysis Populations: Placebo-Controlled Period of PET substudy of Study 301 (upper panel) and Placebo-Controlled Period of PET substudy of Study 302 (lower panel)

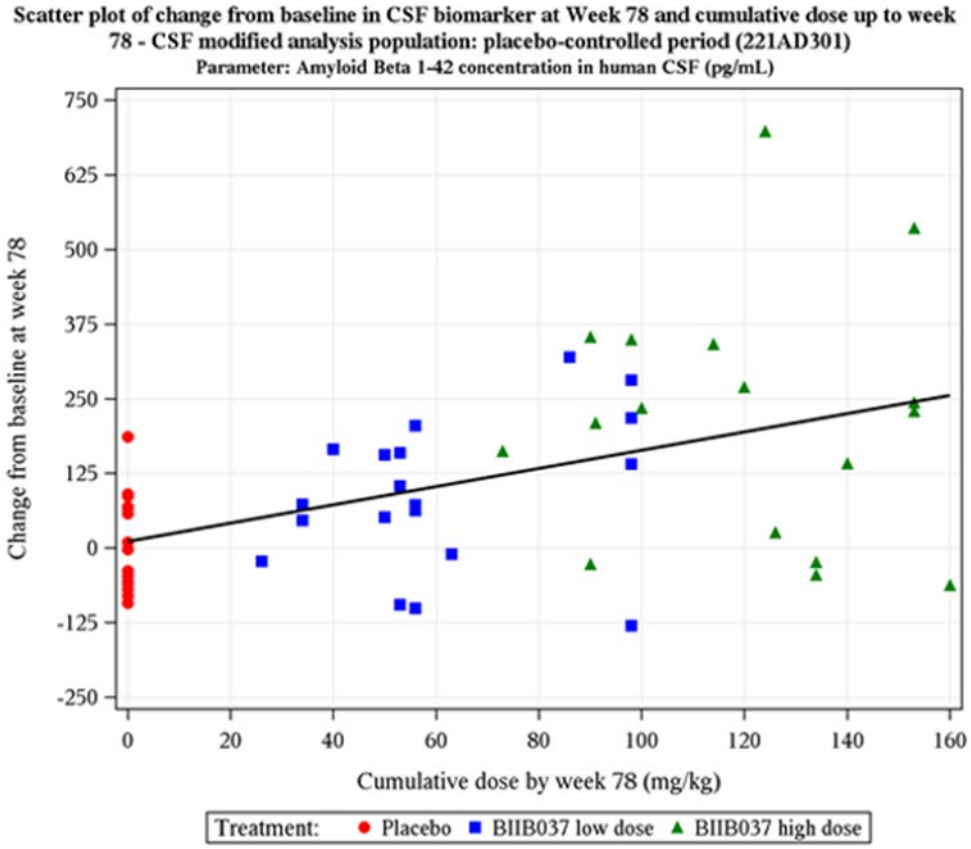


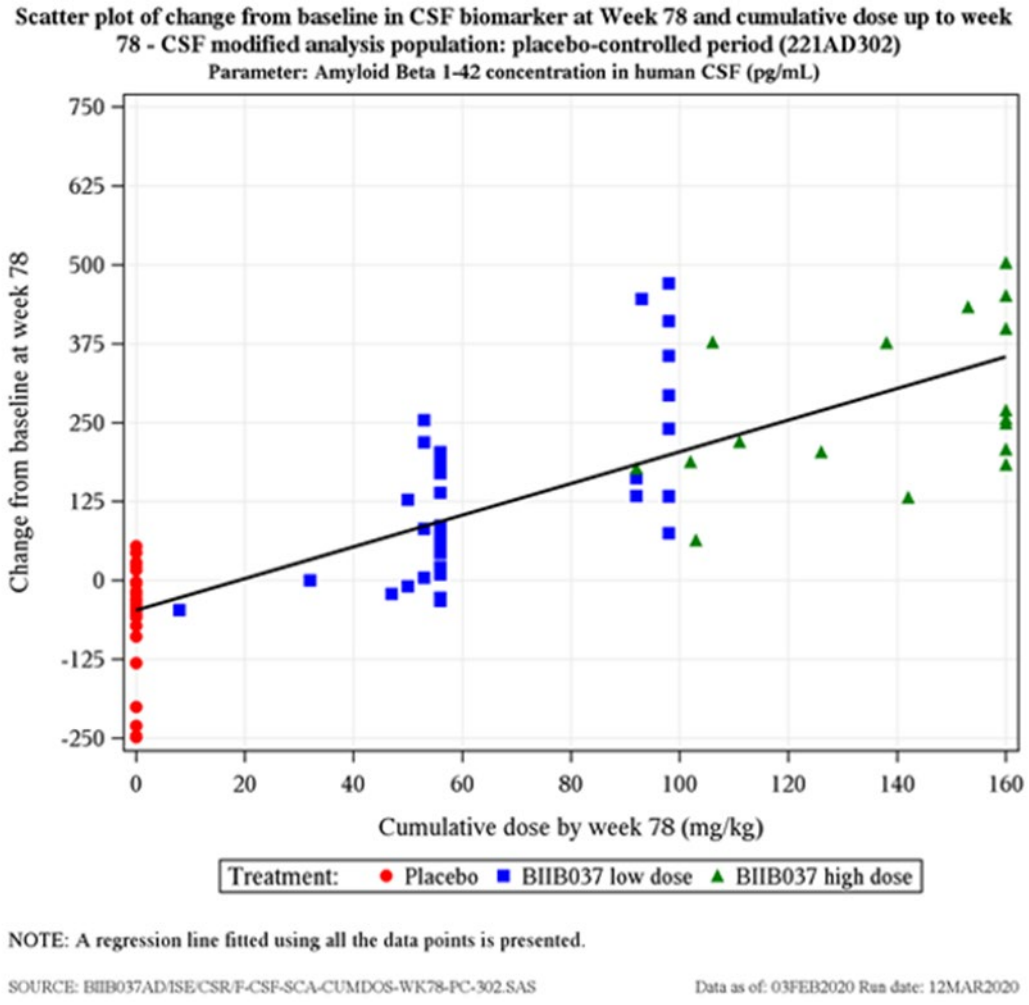
2.5.2.2.3. Secondary pharmacology

The hypothesis at the basis of this development is that aducanumab-mediated amyloid lowering will lead to clinical benefit, and also (perhaps as mediating such benefit) have an impact on other biomarkers - including tau accumulation and neurodegeneration – that are more closely correlated with clinical progression and are postulated to be downstream of amyloid accumulation in the pathophysiological processes.

Measures of CSF levels of Aβ1-42, Aβ1-40, p-Tau and t-tau were conducted in subsamples of Studies 301 and 302. In the subsample of patients in whom CSF Aβ1-42 was investigated, this dose-dependency was less prominent than the PET results. Moreover, there is a large overlap between the doses and the change in CSF Aβ1-42 at week 78, see Figure 8 upper and lower panels. These findings are unexpected, as cerebral clearance of Aβ is associated with an increase of Aβ in the CSF.

Figure 8: Scatter Plot of Change from Baseline in CSF Aβ 1-42 at Week 78 and cumulative dose up to Week 78 – CSF Modified Analysis Population: Placebo-controlled Period of 221AD301 (upper panel) and of 221AD302 (lower panel)





Conflicting results are reported from the investigation of p-tau and t-tau in the CSF, conducted in a subsample of patients from the Phase 3 studies.

In Study 301, no differences in the level of p-tau and t-tau were observed between placebo and aducanumab treatment: the change from baseline in CSF p-Tau levels at Week 78 was -2.24 pg/mL, -13.51 pg/mL, and -13.19 pg/mL for the placebo, low-dose, and high-dose groups, respectively. The difference from placebo at Week 78 was similar in the low dose (-11.27; p=0.2726) and high-dose groups (-10.95; p=0.3019) (n=53). The changes from baseline in CSF t-Tau levels at Week 78 were -33.26 pg/mL, -46.10 pg/mL, and -102.51 pg/mL for the placebo, low and high dose groups, respectively. The difference from placebo at Week 78 was -12.83 pg/mL for the low dose group and -69.25 pg/mL for the high-dose group (p-values: 0.8453 and 0.3098, respectively) (n=48).

In contrast, in Study 302, for both p-tau and t-tau a dose dependent effect was observed. The change from baseline in CSF p-Tau levels at Week 78 was -0.49 pg/mL, -16.13 pg/mL, and -22.93 pg/mL for the placebo, low-dose, and high-dose groups, respectively. The difference from placebo at Week 78 was -15.64 pg/mL (p=0.0035) for the low-dose group and -22.44 pg/mL (p=0.0005) for the high-dose group (n=68). Changes from baseline in CSF t-Tau levels at Week 78 were -0.39 pg/mL, -87.12 pg/mL and -112.44 pg/mL for the placebo, low-dose, and high-dose groups, respectively. The difference from placebo at Week 78 was -86.74 pg/mL (p=0.0148) for the low-dose group and -112.05 pg/mL (p=0.0088) for the high-dose group (n=68).

In preparation to the SAG (see below), the Applicant submitted new data on plasma p-Tau181. According to the Applicant, the data became available after finalisation of the responses to the List of Questions submitted on 11 October 2021. These data were exploratory and concerned N=945 for Study 301 and N=870 for Study 302, who had plasma samples available at baseline and Week 78. In both studies an increase in plasma p-Tau181 for placebo was seen, respectively 9% and 8% (Study 301 and Study 302). In the aducanumab treated patients, a decrease of respectively 16% and 13% (Study 301 and Study 302) for the high dose was found. The low dose seemed to decrease less, in a dose-dependent manner.

Overall, the effect of aducanumab on the (postulated downstream of amyloid accumulation) tau-related biomarkers is not clear, given the contrasting results. It is observed that the changes in tau for the placebo group in Study 301 are not as it would have been expected. A change around 0, or an increase would be expected in the placebo arm since these markers of neural damage - in general – increase with the clinical progression of AD. In addition, data on concentration in the plasma are considered more exploratory and of limited relevance compared to CSF data.

2.5.2.2.4. Exposure/response

Extensive modelling has been performed to describe the exposure-response relationships and to investigate why the estimates of efficacy of aducanumab differed between the Phase 3 studies.

The exposure-response modelling based on CDR-SB data is considered most relevant since it is based on the primary clinical endpoint. The exposure-CDR-SB model consisted of a linear disease progression model on a logit scale with an additive drug effect on the rate of disease progression. The individual average aducanumab serum concentration within a dosing interval (Cavg) was used as an exposure metric in the analysis. The Applicant discussed that Cavg provides a more useful expression of concentration-time relationships than Cmax or Cmin, and is also more biologically relevant as the changes in clinical response were delayed and expected to be due to changes in exposure over the entire concentration-time curve rather than a spot concentration. However, in general, the most relevant exposure metric for mAbs is Ctrough, since this is the parameter associated with receptor binding. In the modelling, the assumption was made that aducanumab affects the rate of disease progression (a disease-modifying effect). According to the Applicant, a symptomatic effect was not detected and the Applicant further argued that this is consistent with the presumed mechanism of action. It is not clear from the reports supplied, that a symptomatic PK/PD model has indeed been tested. Nevertheless, since the effect on CDR score was very small, it will be hard to perform these analyses and this issue is not further pursued.

There were no indications for model misspecifications in the goodness-of-fit plots or the VPCs. The exposure-response model supported the notion of a very small, although concentration-dependent effect in CDR-SB score. There were no major differences in the efficacy of aducanumab between the Phase 3 studies. None of the identified covariates were clinically important. Less than 10 % of the subjects were Asians, for which reason the effect of race should be interpreted with caution.

An indirect response model was developed to describe the effect of aducanumab concentrations on brain Aβ plaque levels (quantified as a composite SUVR, standardized uptake value ratio), with drug acting to induce Aβ plaque elimination. The Applicant provided information on the bootstrap analysis (nonparametric bootstrap analysis). Many of the bootstrap runs failed (533 out of 1000), which indicate that the model is unstable, and therefore cannot be used to draw any conclusions regarding the effect of aducanumab on SUVR. However, additional provided data for the visual predictive checks for the SUVR final model showed that the simulated medians and extreme percentiles (10^{th} and 90^{th}) are in good agreement with the observed medians and percentiles. In addition, parametric bootstrap analysis was

performed which supported the confidence interval from the nonparametric bootstrap analysis. These data support that the exposure-SUVR model is stable and can be used for simulations. Simulations, based on the proposed dose titration to a maintenance dose of 10 mg/kg Q4W, indicated that it would take several years (> 3 years) to approach steady state in SUVR data. Although this model is considered adequate, the results from the modelling have no impact on the benefit-risk assessment.

An exploratory population PK/PD analysis was performed to describe the relationship between SUVR and CDR-SB data. There were limitations with this analysis, SUVR measurements were not performed in two-thirds of the patients, as a consequence the final exposure-SUVR model was used to generate ad hoc model-imputed typical individual predicted SUVR profiles in these subjects. This introduces bias in the modelling and, therefore, the results should be interpreted with caution, and no conclusions can be drawn. Since this analysis was only exploratory, and the estimated effect of aducanumab exposure on CDR-SB score was very small, the issues identified are not further pursued.

2.5.2.2.5. Exposure-safety

Time-to-event (TTE) analyses were performed to predict the hazard for the time of the first ARIA-E (ARIA oedema/effusion) event, and also the hazard for the time for resolution of this event.

The models could reasonably well describe the data. The results indicated an increased risk of ARIA-E at higher aducanumab concentrations and that the risk decreased with time. The ARIA-E hazard was higher during the approximately 200 first days, where the highest fraction of subjects with an event was approximately 0.4. This supports that a dose-titration scheme and frequent monitoring is needed during at least the first 200 days of treatment. The higher ARIA-E hazard during the approximately 200 first days is also in line with the observed ARIA-E incidence, where the majority of first ARIA-E events occurred during the first 8 doses. Baseline hazard seemed higher in ApoE ε4 carriers as compared to non-carriers (1.8 times higher in 1-copy ApoE ε4 and 4 times higher in 2-copy ApoE ε4 carriers). Information was provided regarding the time point for the first event in 1-copy ApoE ε4 carriers, 2-copy ApoE ε4 carriers and non-carriers. The data indicated that the majority of the first ARIA-E event occurred between weeks 12 and 44 in homozygote and heterozygote ApoE ε4 carriers and between weeks 12 and 32 in noncarriers.

The probability of the resolution of the first ARIA-E event increased with time until approximately 80 days. Thereafter the probability of resolution was independent of time. After 100 days, the fraction of subjects without ARIA-E resolution was approximately 0.1-0.3. The results indicated that the aducanumab concentration was a minor contributor to the time to resolution of ARIA-E. The only significant covariate was baseline ARIA-E severity on the baseline hazard. However, since less than 8 % of the patients had severe ARIA-E, the covariate effect in patients with severe ARIA-E at baseline should be interpreted with caution.

The subjects included in the time-to-resolution analysis of an ARIA-E event had no additional ARIA-E events during the time period from the first event and to the resolution of this event.

There are major limitations with the ARIA-E models. These models cannot be used to predict the hazard for an additional ARIA-E event (for instance second/third) in a subject who has already had an ARIA-E event, and also the time for resolution of these additional events. According to the Applicant a repeated time-to-event analysis was not performed since there was a large interindividual variability in the underlying hazard of repeated ARIA-E, which could lead to uncertainties in the model parameter estimates. This is not supported. Uncertainties in parameter estimates could have been reduced by including important covariates. However, the development of a repeated time-to-event model is not pursued further. It is noted that based on the available clinical data, recurrence of ARIA-E cannot be predicted based on any patient or ARIA-related characteristics.

The individual exposures used in the PK/PD analyses, were derived from post hoc parameter estimates from an earlier version of the popPK model (not final PK model). This is considered acceptable since there was only a small difference (<0.1%) in the exposure (Cavg) derived based on the post hoc parameter estimates from the earlier as compared to the final model. There seems to be different covariate relationships between these two models.

2.5.3. Discussion on clinical pharmacology

The pharmacokinetics of aducanumab are typical for an IgG1 mAb drug and characterised by a small central (3.59 l) and peripheral volume distribution (6.04 l), a low clearance (0.0159 l/h), and a long elimination half-life of 24.8 days. Furthermore, linear pharmacokinetics are observed, and a steady-state is achieved after about 4 months. As expected for a mAb, there are no specific issues related to interactions and special patient groups.

The effect on cerebral Aβ load as measured by the PET scan confirms the effect of aducanumab on AD's Aβ pathophysiology. Target engagement of Aβ and proof of concept is considered established. However, the effect of aducanumab on tau-related biomarkers is less clear.

From a clinical pharmacology point of view, there was no major objection to the approval of aducanumab for the proposed indication of treatment of Alzheimer's disease.

2.5.4. Clinical efficacy

The main studies of the clinical development program were study 103, 301 and 302 (Table 1). Study 103 formed the proof of concept study informing the design of the two confirmative studies phase III Studies, i.e. Study 301 and 302. Study 302 is presented by the Applicant as the pivotal study for efficacy accompanied by supportive Studies 103 and 301. This point of view is not endorsed. Studies 301 and 302 were identically designed and planned as Phase 3 studies. Hence, they have the same weight for assessing evidence for efficacy.

The studies are described in Table 1. In the following paragraphs, selection of population and assessment scales are described with reference to the 3 studies together. In the following sections, study 103 is presented first and Studies 301 and 302, given the similarities in design, are presented together.

Selection of the populations

In Study 103, patients were selected by the criteria for AD of the International Working Group (IWG; 2007). In this concept, diagnosis is anchored by the presence of biomarkers, which provide additional certainty to an AD diagnosis in the absence of clear clinical manifestations. In Studies 301 and 302, the patients were selected based on the National Institute on Aging - Alzheimer´s Association (NIA-AA criteria; 2011). According to NIA-AA, biomarkers (e.g. PET-scan) are supportive and not mandatory for diagnosis. Thus, the main difference between the IWG and the NIA-AA-criteria is that following the IWG criteria abnormal biomarkers are required for diagnosis and according to the NIA-AA these support the diagnosis. However, all patients included in the clinical studies had a positive PET-scan for cerebral amyloid. From a regulatory perspective, both the IWG and the NIA-AA sets of criteria are accepted for the diagnosis of AD for research purposes and trial enrichment.

The inclusion based on the extent of cognitive impairment did differ between Study 103 and the phase III studies. In the Phase III studies, a less cognitively impaired population was included. Namely, a narrower range of baseline MMSE scores (24-30, rather than 20-30) was defined, and all participants were required to have a baseline CDR global score of 0.5 (rather than 0.5 or 1).

Table 1: Clinical development program in Marketing Authorisation Application

Study ID **No. of study centres/ locations** **Study period**	**Design** **Objective** **Duration**	**Dose at study initiation***	**Subjects by arm (ITT)** **Subjects in PET-substudy**	**Male/Female** **Age (median; range)** **APOE-ε status** **Diagnosis (Mild AD/MCI)**	**Primary and secondary endpoints**
221AD103 27 centres: US Oct 2012-Jul 2019	Phase 1b RD DB PC MD Safety & tolerability 52 weeks PC + LTE up to 5 years	Fixed: 1, 3, 6, or 10 mg/kg Titration: 1 to 10mg/kg All cohorts were placebo-controlled	196 total: 48 (placebo) 125 (fixed) 23 (titration) 167 total: 42 (placebo) 107 (fixed) 18 (titration)	98/98 73 (51-91) Carrier: 65% Noncarrier: 35% MCI: 43% Mild AD: 57%	Primary: Incidence of (S)AEs e.g. ARIA-E/ARIA-H Secondary: Δ from BL to Week 26 in 18F-florbetapir PET signal
221AD301 169 centres: US/EUR/CAN/ AUS/Asia Aug 2015-Aug 2019	Phase 3 RD DB PC PA Efficacy and safety 8 weeks prior to 1st dose + 78 weeks PC + 18 weeks safety FU / LTE up to 5 years	Low dose after 8wks titration: 3 mg/kg for APOE-ε4 carriers 6 mg/kg for APOE-ε4 non-carriers High dose after 24wks titration: 6 mg/kg for APOE-ε4 carriers 10 mg/kg for APOE-ε4 non-carriers	1647 total: 545 (placebo) 547 (low dose) 555 (high dose) 585 total: 204 (placebo) 198 (low dose) 183 (high dose)	784/863 71 (50-85) Carrier: 69.5% Noncarrier: 30.3% MCI: 80.4% Mild AD: 19.6%	Primary: Δ from BL in CDR-SB at Week 78 Secondary: Δ from BL in MMSE at Week 78 Δ from BL in ADAS-COG13 at Week 78 Δ from BL in ADCS-ADL-MCI at Week 78
221AD302 181 centres: US/EUR/CAN/ Asia Sep 2015-Aug 2019	Phase 3 RD DB PC PA Efficacy and safety 8 weeks prior to 1st dose + 78 weeks PC + 18 weeks safety FU / LTE up to 5 years	Low dose after 8wks titration: 3 mg/kg for APOE-ε4 carriers 6 mg/kg for APOE-ε4 non-carriers High dose after 24wks titration: 6 mg/kg for APOE-ε4 carriers 10 mg/kg for APOE-ε4 non-carriers	1638 total: 548 (placebo) 543 (low dose) 547 (high dose) 488 total: 159 (placebo) 159 (low dose) 170 (high dose)	795/843 72 (50-85) Carrier: 66.8% Noncarrier: 32.8% MCI: 81.6% Mild AD: 18.4%	Primary: Δ from BL in CDR-SB at Week 78 Secondary: Δ from BL in MMSE at Week 78 Δ from BL in ADAS-COG13 at Week 78 Δ from BL in ADCS-ADL-MCI at Week 78

* During studies 301 and 302, the high dose for APOE-ε4 carriers was increased to 10mg/kg based on analyses from cohort 4, study 103 (protocol versions 4-6).

AD = Alzheimer's Disease, ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale, ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment, ApoE ε4 = apolipoprotein E ε4, ARIA-E = amyloid-related imaging abnormality-vasogenic edema, ARIA-H = amyloid-related imaging abnormality-microhemorrhage, macro-hemorrhage, or superficial siderosis, AUS = Australia, BL= baseline, CAN = Canada, CDR-SB = Clinical Dementia Rating-Sum of Boxes, DB = double-blind, EUR = Europe, FU = follow-up, ITT = intent-to-treat, LTE = long term extension, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, OLE = open label extension, PA = parallel group, PC = placebo-controlled, PET = positron emission tomography, PL = placebo, RD = randomised, US = United States, Δ = change.

Assessment scales

The assessment scales used in Studies 103, 301, 302 were the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale (ADAS-Cog), the Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI) and the Neuropsychiatric Inventory-10 (NPI-10).

The assessment scales used in the clinical studies are frequently used in AD. The scales include all domains (cognitive, functional, behavioural and psychiatric) to conclude the clinical relevance of aducanumab in treating AD. In the CHMP guideline for Clinical investigation of medicines for the treatment of Alzheimer's disease (CPMP/EWP/553/95 Rev.2) it is stated that the clinical relevance of an effect on cognition should be confirmed by an effect on function or global clinical assessment in a co-primary endpoint approach. The sensitivity of some scales, especially in the MCI due to AD population, is questioned.

Clinical Dementia Rating – Sum of Boxes (CDR-SB)

The CDR-SB is the primary endpoint in studies 301 and 302. It is a widely used scale in clinical research and in practice. The Clinical Dementia Rating is a global measure comprised of subscales that index the performance of 3 domains of cognition (Memory, Orientation, Judgement and Problem-Solving) and 3 domains of function (Community Affairs, Home and Hobbies, Personal Care) via independent semi-structured interviews with the participant and the informant by a trained rater in order to assess the participant's clinical status. Severity scores are assigned for each of 6 domains ranging from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score). The "sum of boxes" scoring methodology of the CDR sums the score for each of the 6 domains and provides a value ranging from 0 to 18 that can change in increments of 0.5 or greater with higher scores indicating greater disease severity [Morris 1993].

Besides the sum of boxes, the CDR global score is used in clinical and research settings to stage dementia severity. In general, a score of 0 stands for no cognitive impairment, 0.5 for mild cognitive impairment, 1 for mild dementia, 2 for moderate dementia and 3 for severe dementia. The CDR global score is a composite score that combines the 6 box scores using a scoring algorithm that weights memory as the primary domain and all other domains as secondary.

The CDR-SB is a composite endpoint including both cognition and function. The CDR-SB is an acceptable primary endpoint for AD. However, the minimal clinically meaningful difference in change after 104 weeks of treatment is not robustly defined.

Mini Mental State Examination (MMSE)

The MMSE is a performance-based test of global cognitive status widely used in clinical practice and clinical trials. It consists of 11 tests to assess orientation, word recall, attention and calculation, language abilities, and visuospatial ability [Folstein 1975]. When administering the MMSE, the examiner requires the participant to perform tasks that test orientation to time and place, memory, learning and recall, working memory, language and praxis. The scores from the 11 tests were combined to obtain the total score, ranging from 0 to 30, with lower scores indicating greater cognitive impairment.

The sensitivity of the MMSE in MCI due to AD and even some (highly educated) patients with mild AD is questioned. However, on a group level, separation compared to placebo over a prolonged period is expected.

Alzheimer's Disease Assessment Scale - Cognitive Subscale (13 Items) (ADAS-Cog 13)

The ADAS-Cog 13 is a battery of cognitive tasks [Mohs 1997; Rosen 1984]. The scale includes 9 items that test performance (accounting for up to 65 points), as well as 4 clinician-rated items related to language and memory (up to 20 points) with a total score ranging from 0 to 85. An increase in score indicates increased cognitive impairment. The 13 item scale evaluates word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration /distractibility.

The sensitivity of the ADAD-Cog 13 in MCI due to AD and even some (highly educated) patients with mild AD is questioned. Although it has been frequently used before, it is known that this scale is most sensitive in patients in a more advanced stage of disease, and less in mild stages of AD. The Applicant states that for MCI, the Orientation, Word-Recall, Word Recognition, and Number Cancellation tests from the ADAS-Cog 13 have been shown to be sensitive to change; this about half of the ADAS-Cog. Thus, limited effects on both the MMSE and ADAS-Cog-13 may be observed in a double-blind period of 78 Weeks.

Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment [MCI] version) – (ADCS-ADL-MCI)

The ADCS-ADL-MCI is a standard questionnaire that consists of 18 items. It is used in clinical trials to provide an assessment of changes in activities of daily living over time (e.g., shopping, preparing meals, using household appliances, keeping appointments, reading) [Pedrosa 2010]. Informants are asked whether the participant attempted each item in the inventory during the prior 4 weeks and their level of performance. Responses are "Yes", "No", or "Don't Know" with additional sub-questions, numeric ratings, or a choice of multiple elements from a list depending on the item. The total score can range from 0 to 53, with lower values indicating greater impairment.

Interference of activities of daily living (ADL) is measured by the ADCS-ADL-MCI, which is a questionnaire for MCI, and thus also applies for mild AD. Since patients with MCI have often only minor, subtle interference in their activities of daily living, the questionnaire should be able to detect early and small functional changes.

Neuropsychiatric Inventory-10 (NPI-10)

The NPI-10 is a semi-structured interview administered to a knowledgeable informant. The scale is completed by an interviewer with the study partner informant and systematically indexes presence, frequency, and severity of 10 neuropsychiatric domains: delusions, hallucinations, dysphoria, apathy, euphoria, disinhibition, agitation/aggression, irritability/lability, anxiety, and aberrant motor behaviour. For each subdomain, if present, each symptom is further probed and rated for frequency, as well as for its impact on the patient ("severity") and the informant ("caregiver distress"). The total score for each subdomain is calculated by multiplying the frequency and the severity score, yielding a maximum item score of 12. The total NPI score is the sum of all domain scores and ranges from 0 to 120, with higher scores indicating more severe behavioural disturbance.

The use of NPI-10 in this population is subject to limitations. Firstly, the domains that are investigated are more often disturbed in moderate stages of AD. Secondly, problems in the relationship between the informant and the patient may be reflected in the total score.

2.5.4.1. Dose response study

Study 103 was a phase 1b, randomised, double-blind, placebo-controlled multiple-dose study to assess the safety, tolerability, PK and PD of aducanumab in patients with MCI due to AD or mild AD. The safety and tolerability of multiple doses of aducanumab was the primary aim of the study. Amongst the secondary outcomes was the effect of aducanumab on brain amyloid plaque content, and amongst the exploratory efficacy outcomes were change on CDR-SB score and MMSE. The study had a long term extension (LTE) of 5 years.

The study had a staggered, parallel-group design in which patients were enrolled in 4 cohorts. There were 5 dose arms (Table 2). A total of 196 participants were randomised and dosed.

Table 2: Overview of treatments in Study 103

Cohort	# of arms	Placebo	Aducanumab dose	Dose titrated	ApoE ε4 status
1	3	√	1 & 3 mg/kg	-	carriers and non-carriers
2	2	√	10 mg/kg	-	carriers and non-carriers
3	2	√	6 mg/kg	-	carriers and non-carriers
4	2	√	10 mg/kg	√	carriers only

The study protocol was amended to include a dose of up to 30 mg/kg in arms 6 and 7. However, eventually, in these arms 6 mg/kg and placebo were administrated. It was not clearly explained in the submission why the higher doses were not administered. In the placebo-controlled SAD phase I Study 101, doses up to 60 mg/kg were investigated, and the study was concluded that aducanumab was well tolerated at a single dose of up to 30 mg/kg. Based on interim data of Study 103, the fixed 10 mg/kg dose was the most efficacious dose. Given that non-clinical findings seemed to suggest that efficacy seemed to reach a plateau between 10 and 30 mg/kg, and that the risks of ARIAs increased with higher doses, it seems reasonable to decide not to investigate higher doses than the 10 mg/kg dose.

Cohort 4 consisted of ApoE ε4 carriers titrated up to a 10 mg/kg dose because of the incidence of ARIA in the 10 mg/kg cohort. This cohort was added to inform the dose in the Phase III Studies for ApoE ε4 carriers. When the results became available that in carriers receiving aducanumab titrated to 10 mg/kg, the incidence of ARIA-E and discontinuations from treatment due to ARIA-E appeared to be reduced compared with the 10 mg/kg fixed-dose regimen (studied in both ApoE ε4 carriers and noncarriers), the protocols of the ongoing Phase III studies were amended. In these ongoing Phase III studies, the dose in ApoE ε4 carriers of 6 mg/kg was titrated from 6 mg/kg to 10 mg/kg over 24 weeks (see below).

Adverse events

The most common treatment-related adverse events were ARIA-E (24% vs 0% for the total aducanumab group vs patients receiving placebo) and ARIA-H (19% vs 7% for the total aducanumab group vs patients receiving placebo). The incidence of these events was dose-dependent, as reflected in Table 3.

Table 3: Incidence Summary of ARIA Based on Adverse Event eCRF in Arms 1-9: Placebo-Controlled Period

		Aducanumab arms					
	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg	10 mg/kg titration	Total
N	46	31	32	30	32	23	148
ARIA-E	0	1 (3)	2 (6)	11 (37)	13 (41)	8 (35)	35 (24)
ARIA-H	3 (7)	3 (10)	4 (13)	5 (17)	10 (31)	6 (26)	28 (19)

N = Number of dosed subjects with at least one post-baseline MRI

In the majority of subjects, ARIA-E was asymptomatic (63%) and the maximum MRI severity mild (22%) or moderate (59%). This is also the case for ARIA-H events (asymptomatic 80%, MRI severity mild 75%, moderate 14%). ARIA-E resolved on MRI in 44 of 46 participants and was ongoing in 2 participants at the time of the last follow-up.

20 participants reported at least 1 SAE of ARIA during the active treatment period. ARIA-E: 19 participants (10%), ARIA-H superficial siderosis, 6 participants (3%), ARIA-H microhaemorrhage: 4 participants (2%).

Among the 46 participants with incident ARIA-E during the active treatment period, 8 participants had more than 1 episode of ARIA-E: 5 participants had 2 events, 1 participant had 3 events, 1 participant had 4 events, and 1 participant had more than 5 events. Six of the participants with recurrent ARIA-E were in the 10 mg/kg titration group.

The occurrence of symptomatic (e.g. dizziness, confusional state) ARIA-E and ARIA-H was reason to stop treatment as mandated per protocol. However, ARIA management was subject to protocol amendments and changed during the study. In earlier protocol versions, discontinuation of the study was requested in the case of any symptomatic ARIA. In the later protocol versions, patients with ARIA (regardless of severity) were permitted to resume treatment after resolving ARIA-E or stabilisation of ARIA-H. This could have led to more discontinuations under earlier protocol versions than under the later protocol versions.

Exploratory cognitive outcomes

The CDR-SB and MMSE were exploratory efficacy measures. The study should be interpreted with caution given the lack of power, the design including several cohorts recruited in different moments and that could only be randomised to different treatments, and the protocol amendments. In both the 10 mg/kg fixed-dose group and the 10 mg/kg titration group, aducanumab treatment reduced clinical decline as measured with the CDR-SB compared with combined placebo at Week 54, see Table 4. On the MMSE, aducanumab treatment reduced clinical decline compared with combined placebo at Week 54 in the 10 mg/kg fixed-dose group (Table 5).

Table 4: Change from Baseline in CDR-SB by ANCOVA at Week 54: Study 103, Arms 1-9: Placebo-Controlled Period

	Placebo (N=48)	**1 mg/kg (N=31)**	**3 mg/kg (N=32)**	**6 mg/kg (N=30)**	**10 mg/kg Fixed (N=32)**	**10 mg/kg titration (N=23)**
CDR-SB Baseline (mean±SD)	2.7±1.5	3.4±1.8	3.5±2.1	3.1±1.7	3.2±1.8	3.2±1.7
N for analysis	39	23	27	26	23	21
Change on CDR-SB at week 54 (adjusted mean±se)	1.9±0.4	1.7±0.4	1.3±0.4	1.9±0.4	0.63±0.4	0.7±0.5
Difference versus placebo at week 54		-0.20	-0.56	-0.80	-1.26	-1.19
Confidence interval for difference		-1.3;0.1	-1.6;0.5	-1.9;0.3	-2.4;-0.2	-2.3;-0.04
p-value		0.7249	0.2995	0.1398	0.0246	0.0432

Adjusted mean for each treatment group, difference with placebo, 95% confidence interval and p-value were based on ANCOVA model at each timepoint. ANCOVA model was fitted with change from baseline as dependent variable, and with categorical treatment, baseline value and laboratory ApoE status (carrier and non-carrier) as independent variables.

Table 5: Change from Baseline in MMSE by ANCOVA at Week 52: Study 103, Arms 1-9: Placebo-Controlled Period

	Placebo (N=48)	1 mg/kg (N=31)	3 mg/kg (N=32)	6 mg/kg (N=30)	10 mg/kg Fixed (N=32)	10 mg/kg titration (N=23)
MMSE Baseline (mean±SD)	24.7±3.6	23.6±3.3	23.2±4.2	24.4±2.9	24.8±3.1	24.7±3.0
N for analysis	40	25	26	26	25	21
Change on MMSE at week 54 (adjusted mean±se)	-2.45±0.6	-2.2±0.7	-0.75±0.7	-2±0.7	-0.55±0.7	-1±0.9
Difference versus placebo at week 54 (%)		0.25	1.70	0.47	1.91	1.46
Confidence interval for difference		-1.6;2.1	-0.1;3.5	-1.4;2.3	0.06;3.8	-0.5;3.4
p-value		0.7932	0.0700	0.6133	0.0430	0.1496

Adjusted mean for each treatment group, difference with placebo, 95% confidence interval and p-value were based on ANCOVA model at each timepoint. ANCOVA model was fitted with change from baseline as dependent variable, and with categorical treatment, baseline value and laboratory ApoE status (carrier and non-carrier) as independent variables.

The effect of aducanumab on brain amyloid plaque content measured by PET-imaging was a secondary outcome of this study. Please refer to the pharmacodynamics section of this report for the results and discussion of this outcome.

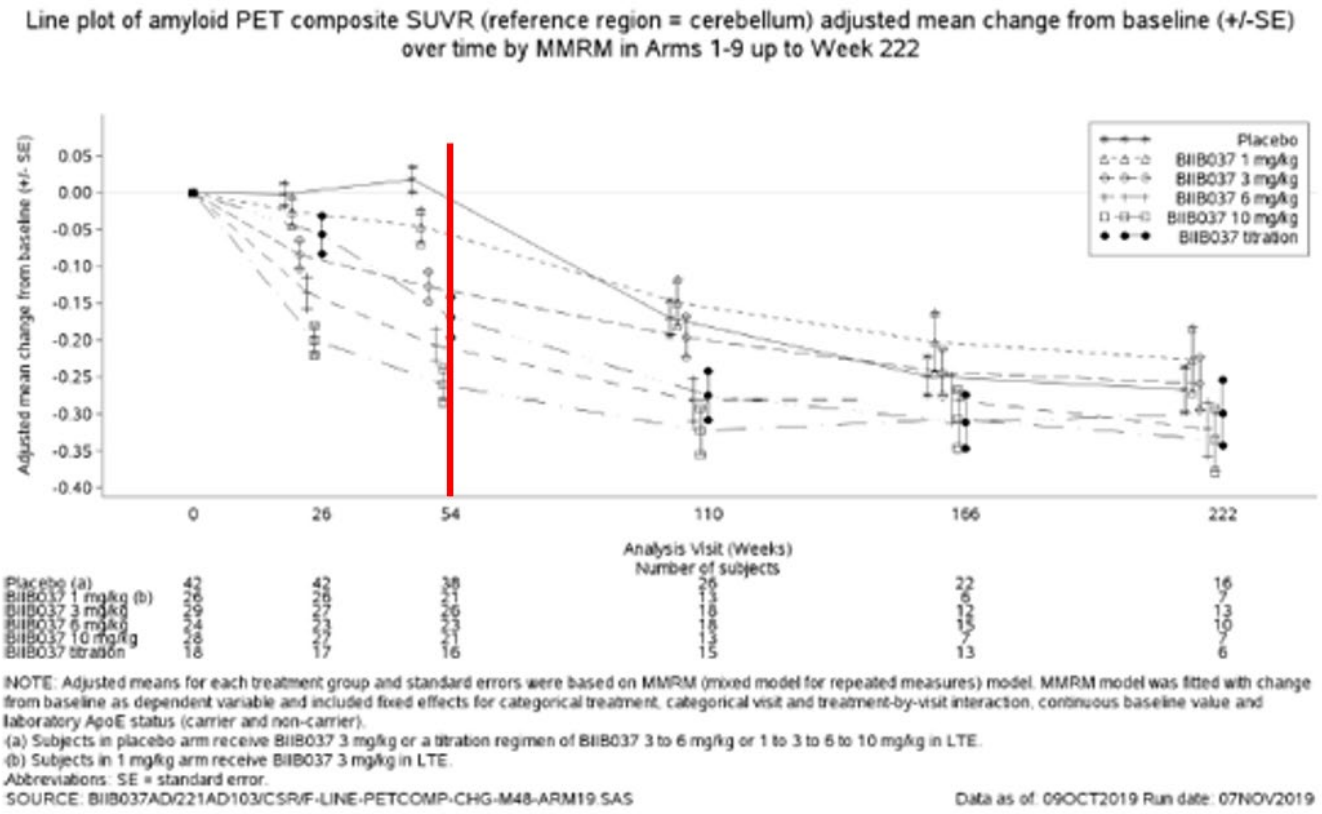
Long-term extension (LTE)

143 patients rolled over into the LTE period of Study 103, continuing to receive the same dose (except for patients receiving 1mg/kg, switched to 3mg/kg). Subjects assigned to placebo in the first phase of the study were switched to the active treatment (either fixed-dose 3 mg/kg, short titration to 6 mg/kg, or long titration to 10 mg/kg).

The LTE was terminated early 21 March 2019 as a result of futility analysis of the two main pivotal studies.

Based on mixed-model repeated measures (MMRM) analysis, cerebral Aβ plaque levels (measured as mean change from baseline in Aβ PET composite SUVR) continued to decline in a time- and dose-dependent manner between Weeks 54 and 110 in patients continuing on Aducanumab. At Week 110, the changes from baseline in the aducanumab 6 mg/kg, 10 mg/kg fixed-dose, and 10 mg/kg titration groups were different from the changes in the placebo/aducanumab groups, see Figure 9. After Week 110, the decline in cerebral Aβ plaque levels seem to stabilise.

Figure 9: Line Plot of Amyloid PET Composite SUVR (Reference Region = Cerebellum) Adjusted Mean Change From Baseline (±SE) Over Time by MMRM in Arms 1-9 up to Week 222 (adjusted by assessor with red line to indicate end of placebo-controlled period)



NOTE: Adjusted means for each treatment group and standard errors were based on MMRM (mixed model for repeated measures) model. MMRM model was fitted with change from baseline as dependent variable and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value and laboratory ApoE status (carrier and non-carrier).
(a) Subjects in placebo arm receive BIIB037 3 mg/kg or a titration regimen of BIIB037 3 to 6 mg/kg or 1 to 3 to 6 to 10 mg/kg in LTE.
(b) Subjects in 1 mg/kg arm receive BIIB037 3 mg/kg in LTE.
Abbreviations: SE = standard error.
SOURCE: BIIB037AD/221AD103/CSR/F-LINE-PETCOMP-CHG-M48-ARM19.SAS Data as of: 09OCT2019 Run date: 07NOV2019

The results of the LTE were consistent with those of the double-blind period. Amyloid load reduction was also observed when patients on placebo switched to active treatment. This further confirms the proof of concept. Based on this study, the most optimal dose is the fixed 10 mg/kg dose, although the highest doses do not seem to plateau. It cannot be excluded that higher doses would be more efficacious.

2.5.4.2. Main studies

Studies 301 and 302

Study Participants

The main Inclusion criteria were:

- Men or women aged 50 to 85 years old, inclusive, at the time of informed consent;
- Had a positive Aβ PET scan. Previously obtained PET scan (within 12 months of Screening) was permissible for participants not participating in the Aβ PET substudy. Previous PET scan images were submitted to the central imaging vendor to confirm study inclusion criteria were met;
- Met all of the following clinical criteria for MCI due to Alzheimer's disease or mild Alzheimer's disease dementia according to NIA-AA criteria and must have:

- A CDR global score of 0.5;

- A Repeatable Battery for Neuropsychological Status (RBANS) score of 85 or lower indicative of objective cognitive impairment (based upon the Delayed Memory Index score). The RBANS Delayed Memory Index score consists of the sum of three verbal delayed memory tasks and one visual memory task;

- A MMSE score between 24 and 30 (inclusive);

- Consented to ApoE ε4 genotyping.

Main Exclusion criteria were:

- Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to Screening;
- Brain MRI performed at Screening (per centrally read MRI) that shows evidence of any of the following: acute or subacute haemorrhage, prior macrohaemorrhage or prior subarachnoid haemorrhage, more than 4 microhaemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis, history of diffuse white matter disease;
- History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.

The in- and exclusion criteria are agreed. Clinical criteria of the NIA-AA were used to confirm MCI due to AD or mild AD. The required scores on the CDR, MMSE and RBANS reflects clinical stages of MCI due to AD and mild AD.

For enrolment into the LTE, patients had to have completed the placebo-controlled period of the study including the Week 78 Visit, to have taken at least 14 doses and not have missed more than 4 consecutive doses, except for patients whose dose was suspended due to ARIA.

Concomitant allowed medication

Medications for chronic conditions (inclusive AD medication) were allowed at a stable dose as long as the participant had been stable on the medication(s) for at least 4 weeks prior to Screening Visit 1 and during the Screening period. AD medication were to be stable for 8 weeks prior to Screening and remain stable during the study. Vaccinations with live or attenuated vaccines were allowed during the study.

Not allowed were 1) medications with platelet anti-aggregant or anti-coagulant properties; except the use of aspirin at a dose of ≤ 325 mg per day, 2) non-prescription narcotic medication, 3) systemic immunosuppressive drugs (including systemic corticosteroids), 4) parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange and plasmapheresis, and 5) any investigational drug.

Treatments

The initially selected doses for Studies 301 and 302 were based on the data available from Cohorts 1 through 3 of Study 103. These data included interim analyses of data from the fixed-dose cohorts (1, 3, 6, and 10 mg/kg).

At the start of the studies (Protocol v1 - Protocol v3), for the 78-week placebo-controlled period of the study, participants were assigned to 1 of 3 study arms in a 1:1:1 ratio (titration to aducanumab low dose, titration to aducanumab high dose, or placebo) based upon their ApoE ε4 carrier status, as follows:

ApoE ε4 carriers

Low dose aducanumab (titration to 3 mg/kg IV Q4W over 8 weeks);

High dose aducanumab (titration to 6 mg/kg IV Q4W over 24 weeks) (Protocol versions 1-3, target dose of 10mg/kg from Protocol Version 4);

Placebo (IV infusion of saline).

ApoE ε4 noncarriers

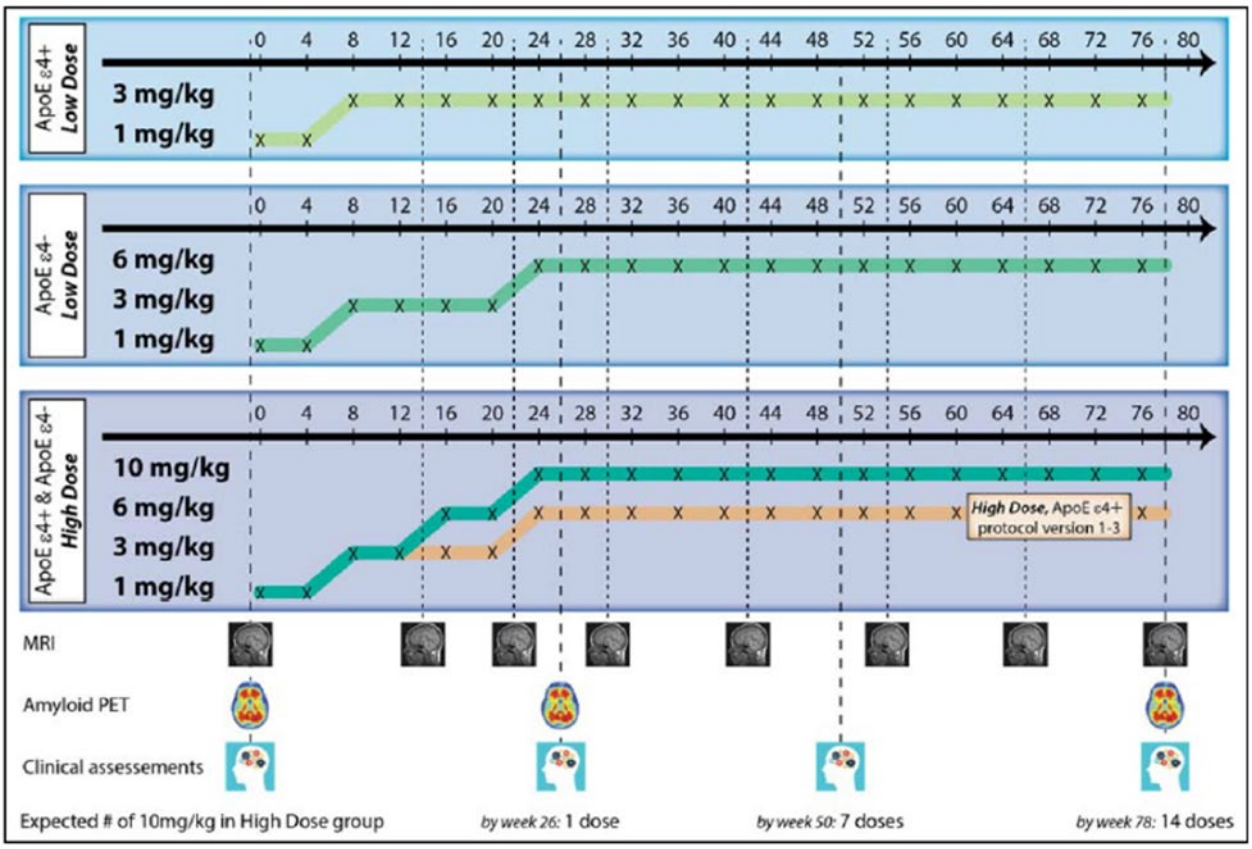
Low dose aducanumab (titration to 6 mg/kg IV Q4W over 24 weeks);

High dose aducanumab (titration to 10 mg/kg IV Q4W over 24 weeks) (all protocol versions);

Placebo (IV infusion of saline).

The reason for a different lower and high dose in ApoE ε4 carriers as compared to ApoE ε4 noncarriers was based on findings in Study 103 demonstrating that the incidence of ARIA was 1) dose-related and 2) higher in ApoE ε4 carriers as compared to ApoE ε4 noncarriers. At the time the Phase III studies were initiated, an additional cohort was added to Study 103, i.e. a cohort with exclusively ApoE ε4 carriers in whom a dose of 10 mg/kg was titrated over 44 weeks. Slow titration up to 10 mg/kg in ApoE ε4 carriers reduced the incidence of ARIA. Because of that, the 6 mg/kg dose regime in ApoE ε4 carriers was changed to 10 mg/kg (protocol version 4). As a result, not all included APOE ε4 carriers received the maximum of 14 doses of 10 mg/kg in the placebo-controlled period compared to the APOE ε4 carriers included after the protocol amendment. Moreover, a group of patients already completed the 78 weeks placebo-controlled period with 6mg/kg dose; this is displayed in the orange line in Figure 10 below. This hampers the interpretation of the efficacy of the high dose.

Figure 10: Schematic of Aducanumab Titration and Dosing in the Phase 3 Programme



Participants who developed ARIA followed a modified treatment schedule. It should be noted that there were changes in ARIA management over time (dose suspension or interruption), as documented in protocol amendments. Overall, the changes were in the direction of allowing more often – in later protocol version – resumed dosing after ARIA. See Table 6 for ARIA management by protocol version.

Table 6: ARIA Management by Protocol Version – Studies 301 and 302

Version 4 (March 2017): ApoE ε4 Carriers Up Titrate to 10 mg/kg		
Version 1 (April 2015)	**Version 3-5 (July 2016-September 2017)**	**Version 6 (June 2018)**
- Asymptomatic, radiographically mild ARIA continue dosing at current dose and schedule[1]	- No change	- No change
- Participants who suspend dosing after an episode of ARIA restart and remain at the next lower dose	- Participants who suspend dosing after 1st ARIA episode to restart at the **same dose**[2]	- No change
- Participants with severe symptomatic ARIA permanently discontinue treatment	- Participants with severe symptomatic ARIA **suspend dosing and resume at the same dose**[2]	- No change
- Participants with serious symptomatic ARIA permanently discontinue treatment	- Participants with serious symptomatic ARIA **(except other medically important**[3]**)** permanently discontinue treatment. **Participants with serious (other medically important**[3]**) ARIA suspend dosing and resume at the same dose**[2]	- No change
- Recurrent ARIA not specifically addressed, managed as the initial episode	- Participants who suspend dosing after a 2nd ARIA **episode to resume at the next lower dose**[2] - Participants who suspend dosing after a 3rd ARIA episode **discontinue treatment**	- Participants who suspend dosing after a 2nd ARIA episode **continue treatment at the same dose**[2] - Participants who suspend dosing after a 3rd ARIA episode **continue treatment at the same dose**[2]
- Participant with radiographically severe ARIA-H (≥10 new incident microhaemorrhages or >2 SS areas permanently discontinue	- Participants with radiographically severe ARIA-H (≥10 new incident microhaemorrhages or >2 SS areas), **or macro-haemorrhage** permanently discontinue	- No change

[1] Suspend dosing only if ARIA becomes symptomatic or radiographically moderate. Radiographically severe ARIA-E also suspends dosing, while severe ARIA-H permanently discontinues.
[2] Following resumption of dosing, titration to continue (if applicable).
[3] "Other medically important events" requiring dose suspension include SAEs that are not life-threatening (in the opinion of the Investigator), do not require inpatient or prolongation of existing hospitalisation, and do not result in significant/permanent disability or congenital anomalies/foetal defects, but may (in the opinion of the Investigator) jeopardise the participant or may require intervention.

Objectives

The primary objective was to evaluate the efficacy of aducanumab in slowing cognitive and functional impairment as measured by changes in the CDR-SB score compared to placebo in participants with early Alzheimer's disease.

The three secondary objectives were to assess the effect of monthly doses of aducanumab compared to placebo on clinical progression as measured by 1) the MMSE, 2) the ADAS-Cog13, and 3) ADCS-ADL-MCI.

The main tertiary objectives were to assess 1) the safety and tolerability of monthly doses of aducanumab, 2) the effect of aducanumab on cerebral amyloid plaque content, 3) the correlation between the primary endpoint and cerebral amyloid plaque content, and 4) the effect of aducanumab on behaviour (NP1-10).

It is acknowledged that the primary objective covers cognition and function. In addition, the rater's overall clinical impression is incorporated in the CDR-SB. The secondary objectives also cover cognition (MMSE and ADAS-Cog 13) and function (ADCS-ADL-MCI). They allow an assessment of the consistency of the results on different cognitive as well as functional scales. Behaviour and neuropsychiatry are covered by the tertiary objective: the NPI-10. The objectives are in line with the CHMP Guideline on AD (CPMP/EWP/553/95 Rev.2) and the CHMP SA received in 2014.

Outcomes/endpoints

Please refer to the introduction of this section for a discussion on the cognitive, functional and behavioural outcome measuring tools.

Primary endpoint:

- Change from baseline in CDR-SB score at Week 78.

Secondary endpoints:

- Change from baseline in MMSE score at Week 78;
- Change from baseline in ADAS-Cog13 score at Week 78;
- Change from baseline in ADCS-ADL-MCI score at Week 78.

Most important tertiary endpoints:

- Incidence of all AEs and SAEs;
- Brain MRI findings, including the incidence of ARIA-E and ARIA-H;
- Change from baseline in Aβ PET signal at 1) Week 26 and 2) Week 78 (in a subset of sites and participants);
- Correlation between the primary endpoint and cerebral Aβ plaque levels as measured by PET imaging over time;
- Change from baseline NPI-10 score at Week 78.

Randomisation and blinding (masking)

Subjects were randomized to receive aducanumab low dose, aducanumab high dose and placebo in a 1:1:1 ratio. The randomization was stratified by site and ApoE ε4 status (carrier or non-carrier). Subjects randomized to placebo at the start of the placebo-controlled period were also randomized to receive dose-blinded aducanumab (low dose: high dose, 1:1 ratio) in the LTE. Enrolment was to be monitored via the IRT, to ensure that the population of subjects with mild AD represented a small percentage of the total enrolled in the trial. Subjects who withdrew from the study could not be replaced.

For the double-blinded placebo-controlled period, all study staff who conducted subject assessments were blinded to the subject treatment assignments: the rating HCPs were blinded to treatment assignment and subject care management and only had access to the information necessary to carry

out their responsibilities. Only pharmacy staff required to manage all aspects of study treatment receipt, dispensing, and preparation were unblinded as a placebo match was not provided for the study.

For the LTE period, the dose information was to remain restricted. The rating and treating HCP were to remain blinded to treatment assignment and only have access to the information necessary to carry out their responsibilities.

Statistical methods

The studies' **sample sizes** were based on results from a protocol-specified interim analysis from Study 221AD103, which included 1-year data from 1, 3, and 10 mg/kg treatment groups. A sample size of 450 subjects per treatment group (1350 in total) was planned to have approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR-SB at Week 78 between the 2 treatment groups. This power calculation was based on a 2-sided t-test assuming equal variance with a final significance level of 0.05, an SD of 1.92, and a drop-out rate of 30%. No justification of the clinical relevance of a difference of 0.5 was provided.

As defined in the prior versions of the protocol, the sample size for these studies was reassessed in a blinded manner approximately 3 months before completion of the initially scheduled enrolment. At the time of this reassessment, about 10.6% of the data was available on the primary endpoint from the combined studies; based on the pooled blinded data from the 2 studies, the SD for the primary endpoint was estimated. As a result of this analysis, the sample size was adjusted from 1350 to 1605 (450 to 535 per treatment) to assure adequate power to detect a mean treatment effect of 0.5.

The **estimand** of the primary analysis is the mean difference of the change from baseline CDR-SB scores at Week 78 between treatment groups in the ITT population. The applicant specified that all observed data was included in the primary analysis, including data collected after intercurrent events, i.e., treatment discontinuation or a change in concomitant use of AD symptomatic medication. This is in line with a treatment policy strategy for all intercurrent events.

The intent-to-treat (ITT) **population** was defined as all subjects who were randomized and received at least 1 dose of study treatment. Subjects were analysed in the groups to which they were randomized.

The per-protocol population was defined as all subjects in the ITT population and also had no mayor protocol violations regarding inclusion criteria (education/work history, PET, diagnosis, previous and concomitant treatment).

All efficacy analyses were performed on the ITT population. In addition, the primary and secondary endpoints were also performed on the per-protocol population. The efficacy analyses were presented by treatment group (per randomization), i.e., aducanumab high-dose, aducanumab low-dose and placebo.

Due to the early futility termination of the studies (see below for details on the futility analysis), the following additional analysis populations were defined:

- Opportunity-to-Complete (OTC) population, defined as the ITT population that have had the opportunity to complete Week 78 by 20 March 2019;
- ITT population during the double-blind period, the ITT population with all the data censored after March 20;
- Uncensored ITT population, the ITT population with all the data collected during the study.

Furthermore, to investigate a posteriori the potential impact of protocol changes leading to different exposures to Aducanumab, the following populations were defined by the Applicant:

- PV3 subset was composed of subjects who consented to protocol version 3 or later version before Week 12;
- PV4 subset was composed of subjects who consented to protocol version 4 or later version before Week 16.

These subsets were not pre-specified.

For the **primary endpoint analysis**, the change from baseline CDR-SB scores was summarized by treatment group at each post-baseline visit. A mixed model repeated measures (MMRM) model was used as the primary analysis to analyse the change from baseline CDR-SB using fixed effects of treatment group, time, treatment group-by-time interaction, baseline CDR-SB, baseline CDR-SB by time interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. An unstructured covariance matrix was used to model the within-patient variance-covariance errors, followed by heterogeneous Toeplitz heterogeneous first-order autoregressive covariance structure in case of non-convergence. In the primary analysis, missing data were assumed to be missing at random.

The following **sensitivity analyses** were performed to assess the robustness of the primary analysis to deviation from the missing-at-random assumption:1) a pattern mixture model (PMM), subjects who withdraw due to reasons that may indicate disease progression was penalized using the copy increment from reference (CIR) method for imputation. After withdrawal due to other reasons, missing data was imputed using the standard multiple imputation method; 2) copy increment from reference (CIR) method was applied to impute the post-withdrawal data for any aducanumab-treated subject who withdraws from study early; 3) after early withdrawal from study, subjects were assumed to exhibit natural disease progression. Natural disease progression was determined based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, using the major inclusion criteria of Studies 221AD301 and 221AD302; and 4) a tipping-point analysis, a range of shift parameters δc and δt were added to the imputed values for subjects on placebo and aducanumab, respectively. The tipping region was defined as the combinations of δc and δt such that the treatment effect is no longer significant.

Several predefined supplementary analyses were performed testing the choice of missing data handling and study population, the number of responders, the slope of progression for different doses, and the primary composite score subcategories.

The **secondary endpoint analysis** for change from baseline MMSE, ADAS-Cog 13 and ADCS-ADL-MCI scores and tertiary change from baseline endpoints were summarized by treatment group at each postbaseline visit. An MMRM model was used as the primary analysis to analyse the change from baseline. The following sensitivity and supplementary analyses that were planned for the primary efficacy endpoint were be conducted for the secondary efficacy endpoints: pattern mixture model, censoring after intercurrent events, per-protocol analysis, slope analysis and divergence effect analysis.

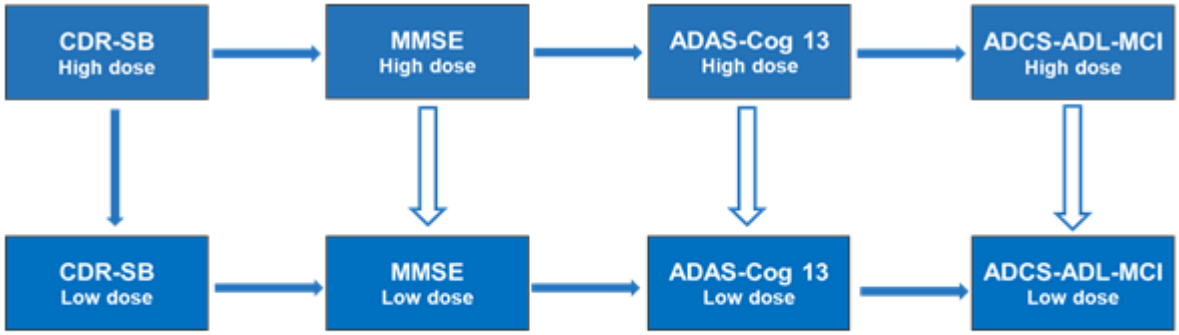
Analyses of primary and secondary endpoints were performed for the following baseline subgroups: ApoE ε4 status, clinical stage, use of AD symptomatic medication, MMSE, region, age and gender.

An **interim analysis for futility**, based on conditional power, occurred after approximately 50% of the subjects completed the Week 78 visit for both studies, performed by an independent group external to Biogen. The conditional power was calculated based on the assumption that the future unobserved treatment effect would be equal to an estimate based on pooled data from Studies 301 and 302. The studies were considered futile when both studies and both high and low dose had conditional power for the primary efficacy endpoint less than 20%.

A sequential (closed) testing procedure (see Figure 11 below) was used to control the overall Type I error rate due to **multiple comparisons**. In this procedure, the primary endpoint was tested for high

dose arm first. If statistically significant, both the primary endpoint for the low dose and the first secondary endpoint for the high dose could be tested at full alpha.

Figure 11: Multiple Testing Procedure of Primary and Secondary Endpoints in Studies 301 and 302



ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR-SB = Clinical Dementia Rating-Sum of Boxes; MMSE = Mini-Mental Status Examination.

Interim analysis and early futility termination

The data cut-off date for the futility analysis was 26 December 2018. As of this date, 945 (57%) patients from Study 301 and 803 (49%) of patients from Study 302 had the opportunity to complete the Week 78 visit. Data from patients who were still active in the studies but did not have the opportunity to complete their Week 78 primary endpoint assessment were not included in calculating conditional power. The independent Data Monitoring Committee (DMC) reviewed the results and, based on the prespecified criteria, recommended to the Applicant that the studies be discontinued, and on 20 March 2019, the Sponsor made the decision to discontinue the programme.

After the futility announcement on 21 March 2019, a full evaluation of a larger dataset was conducted. This dataset, transferred to Biogen on 01 April 2019, contained approximately 10% more participants who completed Week 78 than were available at the time of the futility analysis (which had a data cut-off date of 26 December 2018) and also all data from Weeks 26 and 50 from ongoing participants (approximately 40% of all participants), see Table 7.

Table 7: Datasets Analysed

Dataset	Participant Population	Study 301 n (%)	Study 302 n (%)	Studies 301+302 n (%)
Interim Futility	Opportunity-to-Complete	945 (57%)	803 (49%)	1748 (53%)
April Transfer	Opportunity-to-Complete	1084 (66%)	982 (60%)	2066 (63%)
	ITT [b]	1647 (100%)	1638 (100%)	3285 (100%)
	PET sub-study	582 (35%)	485 (30%)	1067 (32%)

Abbreviations: ITT = intent to treat; PET = positron emission tomography

[a] Participants who have had the opportunity to complete week 78 visit by the time of the cutoff data for that dataset.

[b] All participants' data (data after March 20 are censored for efficacy analyses). Note: data cleaning was ongoing for a small amount of data at the time of the April analysis.

Data source: Appendix G3A Table 1

The April Transfer ITT censored analysis is the ITT population, excluding the data collected after 20 March 2019. This population is the main population discussed in this assessment report since the data collection for this group of overrunning patients was still conducted in a double-blinded manner and in the same manner as before the futility analysis. This is in line with the *Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design.* However, in line with the same Reflection paper, the results on the interim analysis dataset – where discordant – shall also be briefly presented.

Results – Study 301

Participant flow – Study 301

Planned: 1605 patients.

Randomized: 1653 patients were randomized (548 patients to placebo, 549 patients to aducanumab low dose and 556 to aducanumab high dose) and 1647 were dosed.

Completed: 938 (57%) patients completed the study (325 (59.6%) patients on placebo and 325 (59.4%) patients on aducanumab low dose and 288 (51.9%) on aducanumab high dose).

Date first patient dosed: 13 August 2015

Date last patient dosed: 20 March 2019

Date last safety follow-up visit: 8 August 2019

The US was the SAP-defined region where the largest number of participants were randomized and dosed (n = 763), followed by Europe/Canada/Australia (n = 721) and Asia (n = 163).

Data on screening failures were provided upon request. In total, there were 4520 screening failures. The Applicant explained that the majority of screening failures (n=3023, 66.9%) was because patients did not meet the clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria, or did not meet the requirements of the cognitive screenings outcomes. 13.3% (n=599) of screening failures were

patients with a negative PET scan. In 2.8% (n= 128) of cases the reason for exclusion was brain MRI findings at screening.

More than 40% of the randomized patients did not complete the study. The most common reason for discontinuation/withdrawal from the study was 'other'. This coding was, in the majority of cases, indicating the non-completion due to termination of the study. The second most reason for not completing the study was 'adverse event'. This was the case in a dose-dependent manner: for 5.1% of placebo, 8.2% of the low-dose and 11.4% of the high-dose. A small number of patients discontinued because of disease progression.

Since the high dose for ApoE ε4 carriers was amended, only 6.1 % of the ApoE ε4 carriers assigned to high dose received all 14 doses of 10 mg/kg. On the other hand, 33.5% of ApoE ε4 noncarriers assigned to high dose received all 10 mg/kg doses.

Baseline data – Study 301

The included study population represents a population of MCI due to AD and mild AD, in population and clinical characteristics. There were no relevant differences between treatment groups regarding demographics and baseline disease characteristics (Table 8, Table 9). Slightly over 2/3 of patients were APOE ε4 carriers, the main known genetic risk factor of AD. This is in line with the percentage of APOE ε4 carriers in confirmed AD.

In total, 56.4% of the patients used cholinesterase inhibitors and/or memantine at baseline. Moreover, 13% of the patients stopped symptomatic AD treatment prior to entering the study.

Table 8: Participant Demographics and Baseline Disease Characteristics—Final Dataset, ITT Population – Study 301 (symptomatic AD medication added by the assessor)

	Placebo (N=545)	Low dose (N=547)	High dose (N=555)	Total (N=1647)
Age in years, mean ± SD	69.8±7.72	70.4±6.96	70.0±7.65	70.1±7.45
Sex, Female n (%)	287 (52.7)	284 (51.9)	292 (52.6)	863 (52.4)
Race				
Asian n (%)	55 (10.1)	55 (10.1)	65 (11.7)	175 (10.6)
White n (%)	413 (75.8)	412 (75.3)	413 (74.4)	1238 (75.2)
Education years, mean ± SD	14.7±3.66	14.6±3.77	14.6±3.72	14.6±3.71
AD medications used, n (%)	299 (54.9)	317 (58.0)	313 (56.4)	929 (56.4)
ApoE ε4, n (%)				
Carriers	376 (69.0)	391 (71.5)	378 (68.1)	1145 (69.5)
Homozygote ε4	104 (19.1)	101 (18.5)	104 (18.7)	309 (18.8)
Heterozygote ε4	272 (49.9)	290 (53.0)	274 (49.4)	836 (50.8)
Non-carriers	167 (30.6)	156 (28.5)	176 (31.7)	499 (30.3)
Clinical stage, n (%)				
MCI due to AD	443 (81.3)	440 (80.4)	442 (79.6)	1325 (80.4)
Mild AD	102 (18.7)	107 (19.6)	113 (20.4)	322 (19.6)
(n) – PET substudy	(204)	(198)	(183)	(585)
PET SUVR, mean composite ± SD	1.376±0.1990	1.385±0.1859	1.407±0.1786	1.389±0.1885
Symptomatic AD medication, n (%)	299 (54.9)	317 (58)	313 (56.4)	929 (56.4)

Cholinesterase inhibitors, n (%)	242 (44.4)	257 (47.0)	264 (47.6)	763 (46.3)
Memantine, n (%)	16 (2.9)	15 (2.7)	13 (2.3)	44 (2.7)
Both, n (%)	41 (7.5)	45 (8.2)	36 (6.5)	122 (7.4)
AD medication stopped at entry, n (%)	71 (13)	77 (14.1)	66 (11.9)	214 (13)

AD = Alzheimer's disease; ApoE ε4 = apolipoprotein E ε4; MCI = mild cognitive impairment; n = number; PET = positron emission tomography; SD = standard deviation

Data source: Appendix G2 Table 2, Table 3, Table 4, and Table 5, CSR Study 301

Table 9: Baseline Clinical Scores—Final Dataset, ITT Population – Study 301

	Placebo (N=545)	Low dose (N=547)	High dose (N=555)	Total (N=1647)
RBANS delayed memory score, mean ± SD	60.0±13.65	59.5±14.16	60.6±14.09	60.0±13.97
MMSE, mean ± SD	26.4±1.73	26.4±1.78	26.4±1.77	26.4±1.76
CDR Global Score, n (%)				
0.5	544 (99.8)	546 (99.8)	554 (99.8)	1644 (99.8)
1	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)
CDR-SB, mean ± SD	2.40±1.012	2.43±1.014	2.40±1.010	2.41±1.012
CDR cognitive subscore, mean ± SD	1.73±0.623	1.75±0.615	1.72±0.613	1.73±0.617
CDR functional subscore, mean ± SD	0.68±0.574	0.68±0.558	0.68±0.585	0.68±0.572
ADAS-Cog 13, mean ± SD	22.5±6.56	22.5±6.30	22.4±6.54	22.5±6.46
ADCS-ADL-MCI score, mean ± SD	43.0±5.55	42.9±5.73	42.9±5.70	42.9±5.66

ADAS-Cog 13 =Alzheimer's Disease Assessment Scale – Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR-SB = Clinical Dementia Rating – Sum of Boxes; ITT = intent-to-treat; MMSE = Mini-Mental State Examination; PBO = placebo; n = number; RBANS = Repeatable Battery for Neuropsychological Status

Data source: Appendix G2 Table 4

585 patients participated in the PET sub study: 204 on placebo, 198 on the low dose and 183 on the high dose. There were no relevant differences between treatment groups in the PET sub study regarding demographics and baseline disease characteristics. This subsample appears a good reflection of the overall study population.

Numbers analysed – Study 301

Please refer to Table 9 above for numbers analysed.

Outcomes and estimation – Study 301

Primary endpoint

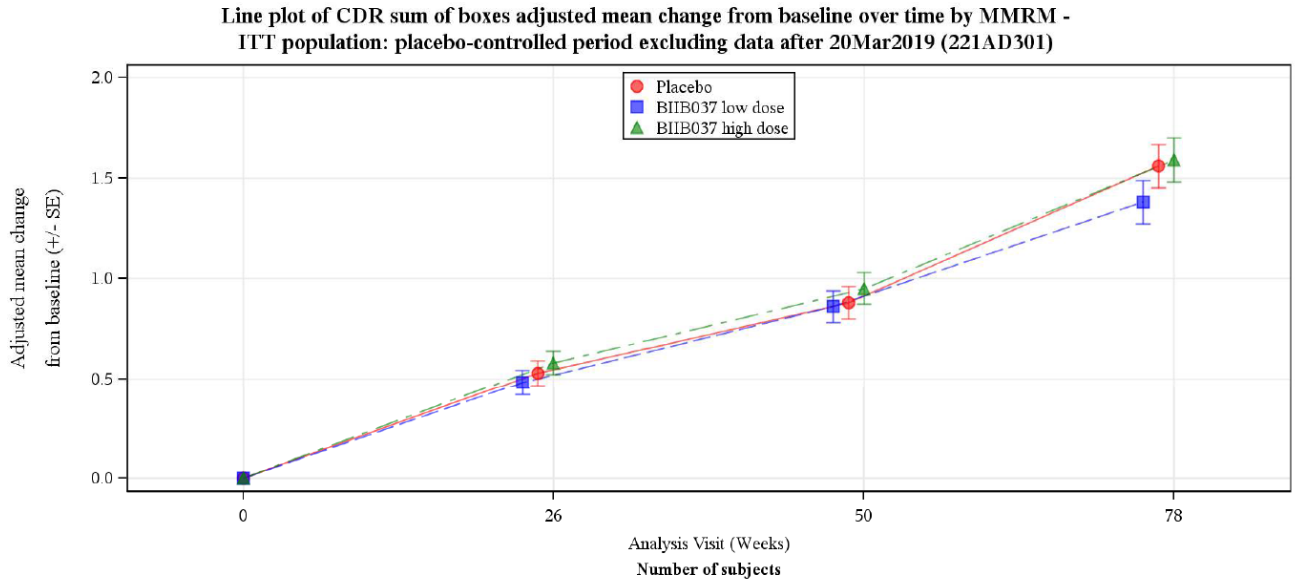
The primary endpoint was Change from Baseline in CDR-SB at Week 78, see Table 10 and Figure 12 for results. Results for the high-dose group show no difference in clinical decline compared with placebo (p =0.8330).

Table 10: Change from Baseline in CDR-SB at Week 78: Study 301, ITT Censored Analysis, (made by the assessor)

	Placebo (N=545)	Low dose (N=547)	High dose (N=555)
CDR-SB Baseline (mean±SD)	2.40±1.012	2.43±1.014	2.40±1.010
CDR-SB at week 78 (mean±SD)	3.95±2.340	3.85±2.210	4.00± 2.518
Change on CDR-SB at week 78 (adjusted mean±SE)	1.56±0.108	1.38±0.108	1.59±0.111
Difference versus placebo at week 78 (%)		-0.18 (-12%)	0.03 (2%)
Confidence interval for difference		-0.469;0.110	-0.262;0.326
p-value		0.2250	0.8330

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 12: Line Plot of CDR-SB Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 26NOV2019

Domain Analysis of CDR

The difference between the aducanumab high-dose group and the placebo group based on change from baseline on the CDR **cognitive** subscore at Week 78 was 0.02 (2% compared to placebo, p=0.7944). The difference between the aducanumab low-dose group and the placebo group was -0.10 (-12% compared to placebo, p=0.2073).

The difference between the aducanumab high-dose group and the placebo group based on change from baseline on the CDR **functional** subscore at Week 78 was 0.01 (1% compared to placebo, p=0.9525). The difference between the aducanumab low-dose group and the placebo group was -0.07 (-10% compared to placebo, p=0.3970).

Overall, 67.8% (high-dose) and 67.7% (low-dose) of patients had a global CDR-score of 0.5 at the Week 78 visit compared with 64.0% of patients in the placebo group. This means that these patients showed no progression on this global score since a global CDR-score of 0.5 was required for study inclusion.

Secondary endpoints

Note that because of the results on the primary endpoints, result on the secondary endpoints cannot be claimed being significant given the closed test procedure. Results of secondary endpoints (Tables 11-13 and Figures 13-15) presented are purely descriptive and not consistent.

No differences between placebo and the two treatment arms of aducanumab were observed after 78 weeks in any of the secondary endpoints.

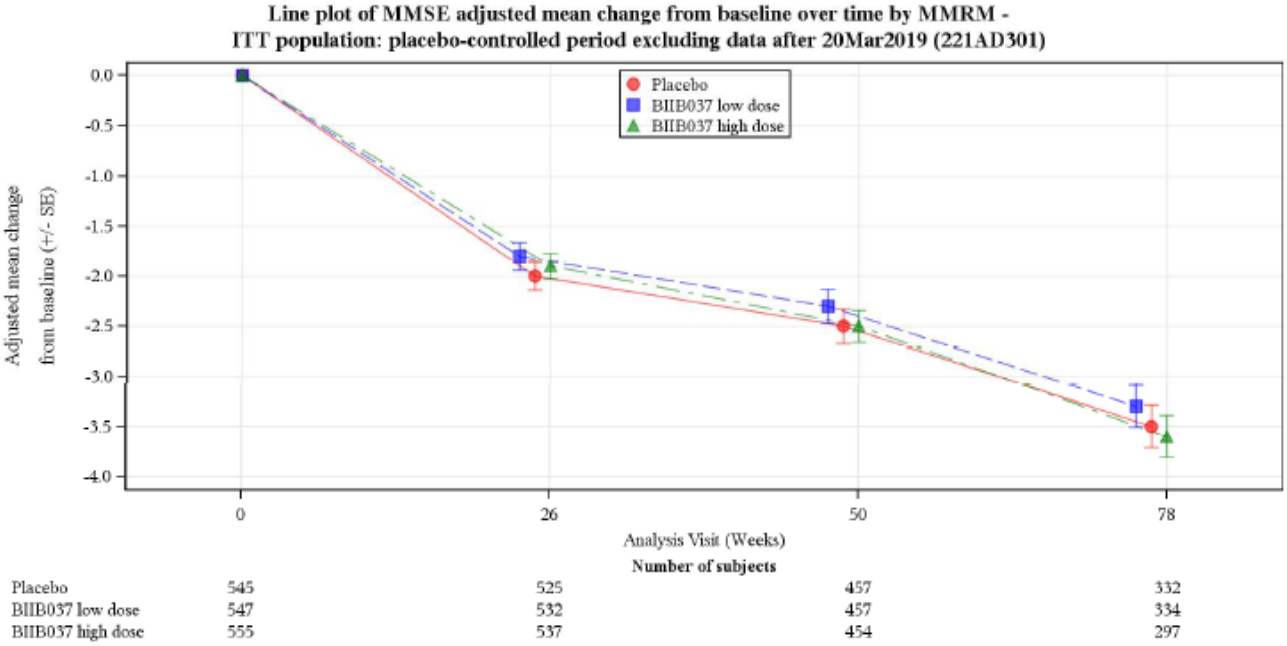
Change from baseline in MMSE score at Week 78

Table 11: Change from Baseline in MMSE at Week 78: Study 301, ITT Censored Analysis (made by the assessor)

	Placebo (N=545)	**Low dose** (N=547)	**High dose** (N=555)
MMSE Baseline (mean±SD)	26.4±1.73	26.4±1.78	26.4±1.77
MMSE at week 78 (mean±SD)	23.1±4.18	23.3±4.42	22.9±4.58
Change on MMSE at week 78 (adjusted mean±se)	-3.5±0.21	-3.3±0.21	-3.6±0.21
Difference versus placebo at week 78 (%)		0.2 (-6%)	-0.1 (3%)
Confidence interval for difference		-0.35;0.74	-0.62;0.49
p-value		0.4795	0.8106

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 13: Line Plot of MMSE Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



Number of subjects

Placebo	545	525	457	332
BIIB037 low dose	547	532	457	334
BIIB037 high dose	555	537	454	297

NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in MMSE as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline MMSE value, baseline MMSE by visit interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 26NOV2019

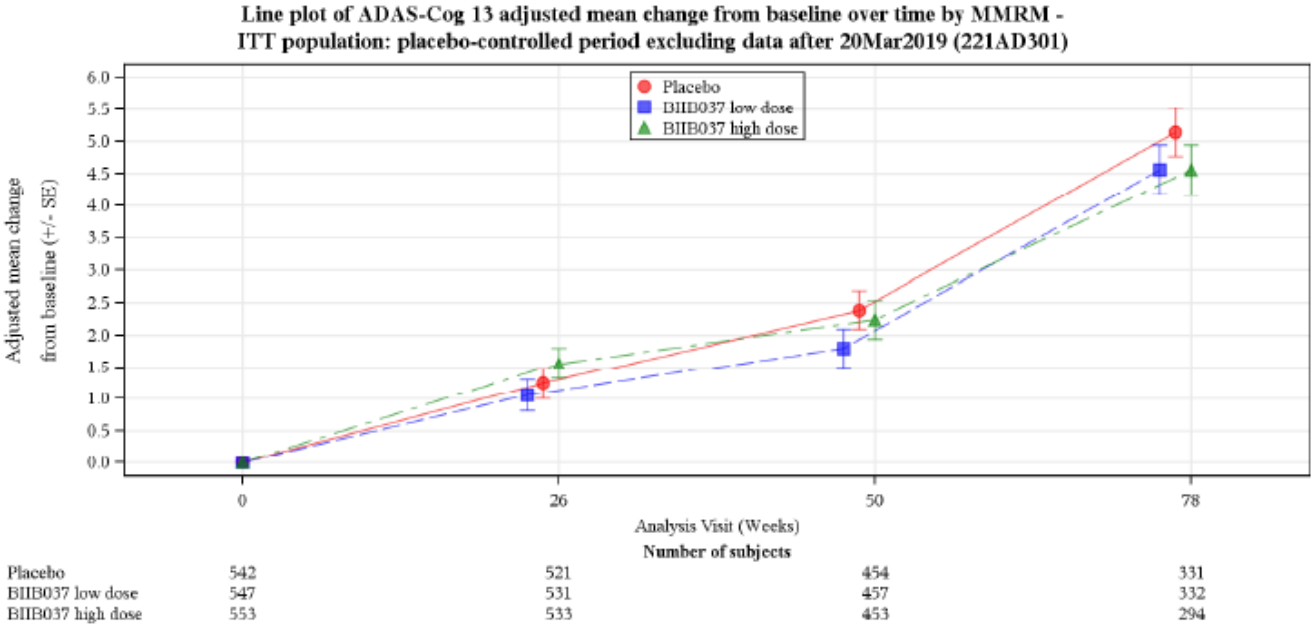
Change from baseline in ADAS-Cog13 score at Week 78

Table 12: Change from Baseline in ADAS-Cog13 at Week 78: Study 301, ITT Censored Analysis (made by the assessor)

	Placebo (N=545)	Low dose (N=547)	High dose (N=555)
ADAS-COG Baseline (mean±SD)	22.5±6.56	22.5±6.30	22.4±6.54
ADAS-COG at week 78 (mean±SD)	27.3±10.11	27.09±9.95	27.2±9.62
Change on ADAS-COG at week 78 (adjusted mean±se)	5.14±0.38	4.56±0.38	4.55±0.39
Difference versus placebo at week 78 (%)		-0.58 (-11%)	-0.59 (-11%)
Confidence interval for difference		-1.58;0.42	-1.61;0.43
p-value		0.2536	0.2578

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 14: Line Plot of ADAS-Cog13 Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 201



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in ADAS-Cog 13 as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 26NOV2019

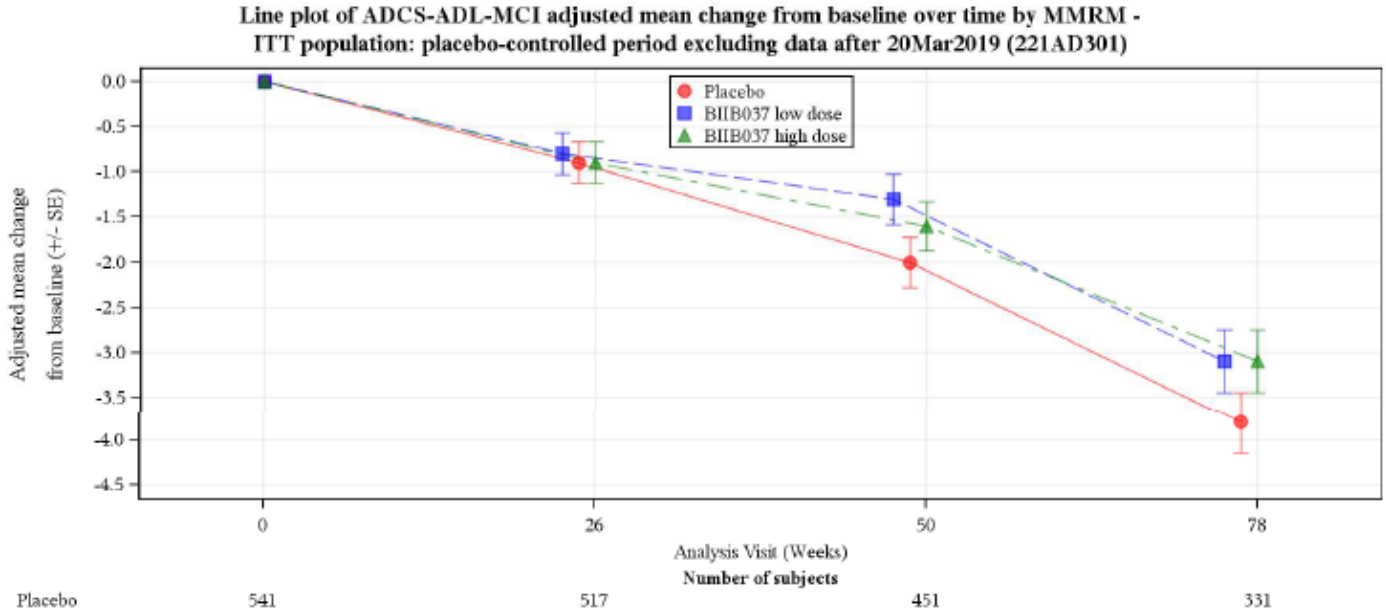
Change from baseline in ADCS-ADL-MCI score at Week 78

Table 13: Change from Baseline in ADCS-ADL-MCI at Week 78: Study 301, ITT Censored Analysis (made by the assessor)

	Placebo (N=545)	Low dose (N=547)	High dose (N=555)
ADCS-ADL-MCI Baseline (mean±SD)	43.0±5.55	42.9±5.73	42.9±5.70
ADCS-ADL-MCI at week 78 (mean±SD)	39.4±8.05	39.8±7.65	40.2±8.3
Change on ADCS-ADL-MCI at week 78 (adjusted mean±se)	-3.8±0.35	-3.1±0.35	-3.1±0.35
Difference versus placebo at week 78 (%)		0.7 (-18%)	0.7 (-18%)
Confidence interval for difference		-0.19;1.64	-0.25;1.61
p-value		0.1225	0.1506

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 15: Line Plot of ADCS-ADL-MCI Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in ADCS-ADL-MCI as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 26NOV2019

Most important tertiary endpoints

Change from baseline NPI-10 score at Week 78

No difference between placebo and the high dose aducanumab were observed after 78 weeks on NPI-10, a measure of behaviour. An 83% reduction in clinical decline was observed for the low dose group compared with placebo, see Table 14.

Table 14: Change from Baseline in NPI-10 at Week 78: Study 301, ITT Censored Analysis (made by the assessor)

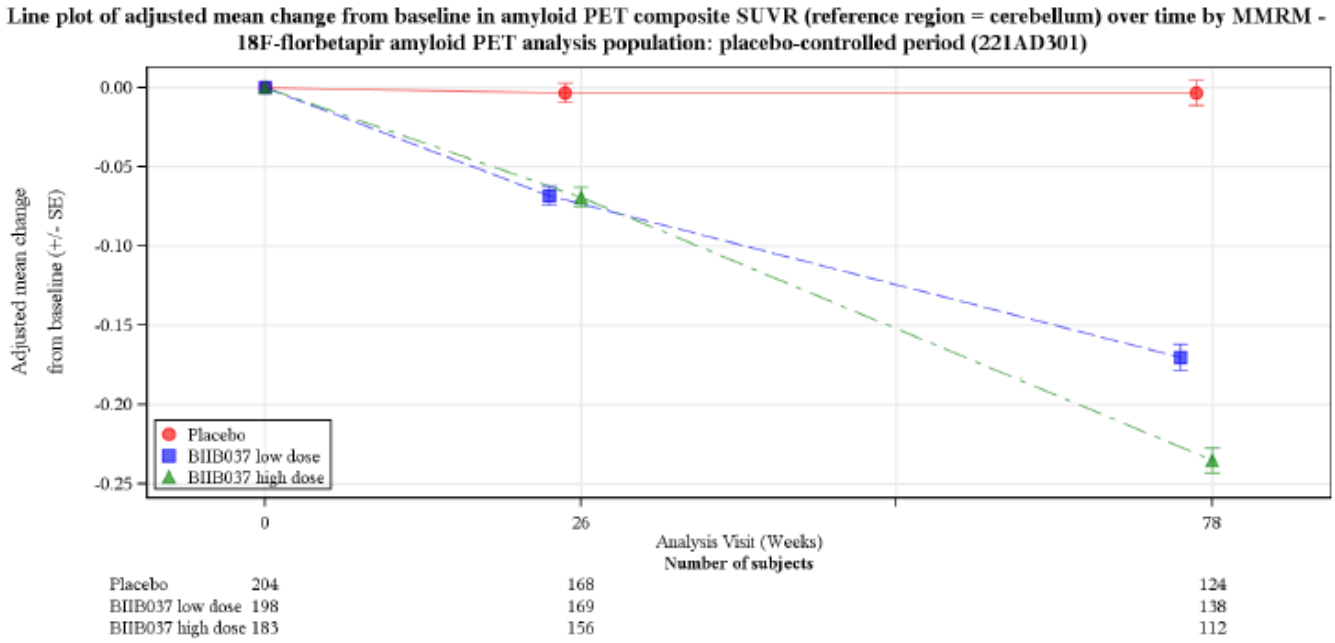
	Placebo (N=545)	**Low dose** (N=547)	**High dose** (N=555)
NPI-10 Baseline (mean±SD)	4.7±6.69	4.9±6.75	4.6±6.68
NPI-10 at week 78 (mean±SD)	5.9±8.24	5.0±6.59	6.0±8.66
Change on NPI-10 at week 78 (adjusted mean±se)	1.2±0.39	0.1±0.39	1.2±0.40
Difference versus placebo at week 78 (%)		-1.0 (-83%)	0.1 (8%)
Confidence interval for difference		-2.06;-0.02	-0.98;1.10
p-value		0.0460	0.9071

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Change from baseline in Aβ PET signal

Around 35% of the total sample was included in the PET sub-study. The adjusted mean change from baseline in Aβ PET composite SUVR relative to placebo was statistically significant in favour of aducanumab at both the low and high dose at Week 26 (high dose: -0.066 [-15.225], p<0.0001; low dose: -0.065 [14.982], p<0.0001) and Week 78 (high dose: -0.232 [53.472], p<0.0001; low dose: -0.167 [38.476], p<0.0001), see **Figure 17**Figure 16.

Figure 16: Line Plot of Adjusted Mean Change From Baseline in Amyloid PET Composite SUVR (Reference Region = Cerebellum) Over Time by MMRM – 18F-Florbetapir Amyloid PET Analysis Population: Placebo-Controlled Period



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in SUVR as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR value, baseline SUVR value by visit interaction, baseline MMSE, baseline age and laboratory ApoE status.

SOURCE: BIIB037AD/221AD301/CSR/F-PET-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 26NOV2019

Correlation of Aβ and primary endpoint

Table 15 shows the correlation and partial correlation for change from baseline amyloid PET composite SUVR versus change from baseline CDR sum of boxes at Week 78. A negligible association between change in cerebral amyloid-beta load and change in the primary endpoint was found.

Table 15: Correlation and partial correlation for change from baseline amyloid PET composite SUVR (reference region = cerebellum) versus change from baseline CDR sum of boxes at Week 78 – 18F-florbetapir amyloid PET analysis population: placebo-controlled period excluding efficacy data after 20Mar2019 (Study 301), made by the assessor

	Placebo	Aducanumab low dose	Aducanumab high dose	Total
N evaluable for correlation analysis	139 (68.1)	146 (73.7)	123 (67.2)	269 (70.6)
Pearson correlation **95% CI** **p-value**	-0.05 (-0.211, 0.121) 0.5875	-0.01 (-0.167, 0.157) 0.9512	0.07 (-0.110, 0.242) 0.4561	0.03 (-0.088, 0.150) 0.6079
Spearman correlation **95% CI** **p-value**	-0.06 (-0.228, 0.104) 0.4550	0.01 (-0.151, 0.173) 0.8929	0.09 (-0.085, 0.266) 0.3069	0.05 (-0.069, 0.170) 0.4022
Partial Pearson correlation **95% CI** **p-value**	-0.06 (-0.221, 0.113) 0.5208	-0.03 (-0.192, 0.135) 0.7255	0.08 (-0.102, 0.253) 0.3959	0.04 (-0.083, 0.157) 0.5407
Partial Spearman correlation **95% CI** **p-value**	-0.06 (-0.230, 0.104) 0.4531	-0.01 (-0.177, 0.150) 0.8656	0.09 (-0.092, 0.262) 0.3375	0.04 (-0.075, 0.164) 0.4646

NOTE: Partial correlations are calculated adjusting for baseline amyloid PET SUVR and baseline CDR sum of boxes.

Long-term extension

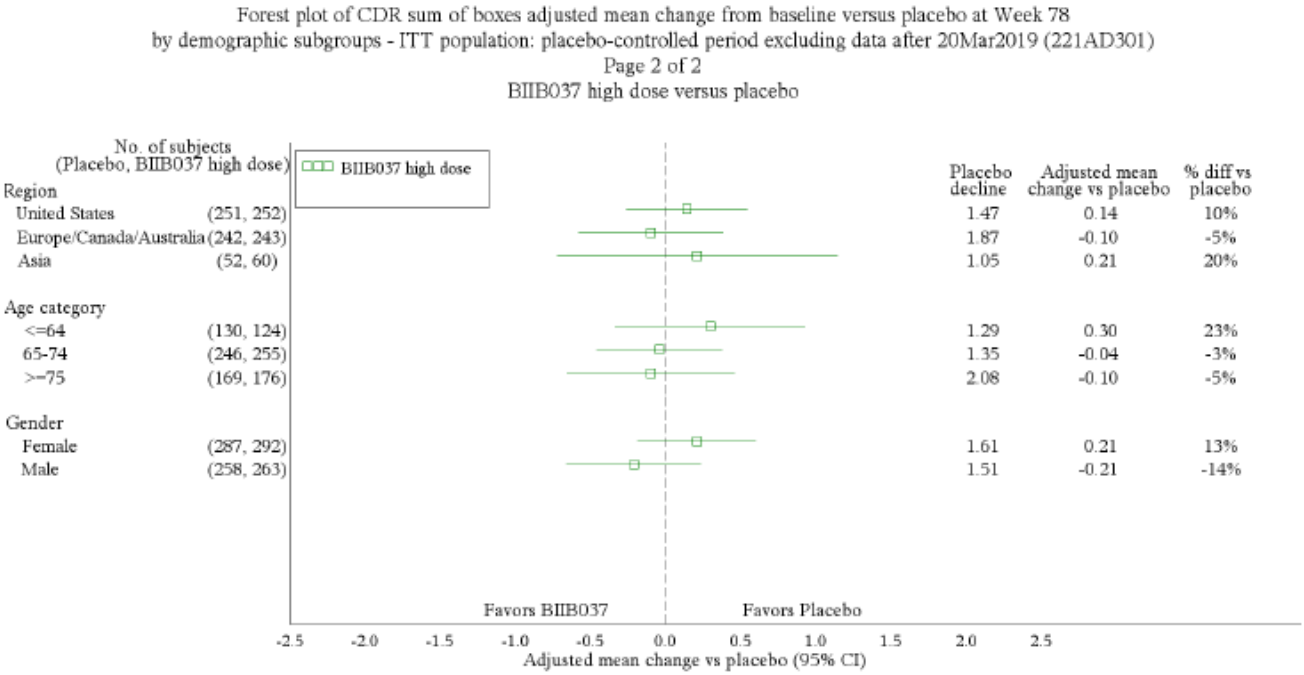
302 Patients on placebo, 299 on aducanumab low dose and 251 on aducanumab high dose rolled over into the LTE (N=852, 51.7% of the cohort randomized in the placebo-controlled period). During the LTE period, participants who were randomized to aducanumab (low-dose or high-dose) in the placebo-controlled period continued to receive aducanumab on the same dose *('early start', remained on aducanumab*) and participants who were randomized to placebo during the PC period were switched to receive aducanumab (high-dose or low-dose as randomized at study entry; '*late start', placebo → aducanumab'*).

Since the study terminated early, data up to 56 weeks -with small numbers of patients- in addition to the 78 weeks RCT are available instead of data up to 5 years. This limits the interpretation of the long term treatment effect of aducanumab in MCI due to AD and mild AD. On the CDR-SB, no differences in change from baseline between the 'remained on aducanumab' high-dose group compared to the 'placebo → aducanumab' high-dose group at Weeks 78 (end of placebo-controlled phase), 106 and 134 were observed. This was also the case for the 'remained on aducanumab' low-dose compared to the 'placebo → aducanumab' low-dose. Upon visual inspection, the change in the long term in the early start high-dose group seems to increase more than the change in the late start high-dose group, after rolling over on active treatment. In general, a similar pattern on the secondary endpoints was observed.

Subgroup analyses

Figure 17 and Figure 18 show forest plots of the primary endpoint for subgroups according to demographic and baseline characteristics. Results of the subgroup are irregular and appear at random. Within the subgroups favour placebo as often as it favours aducanumab. This is suggestive for the absence of a true treatment effect in Study 301.

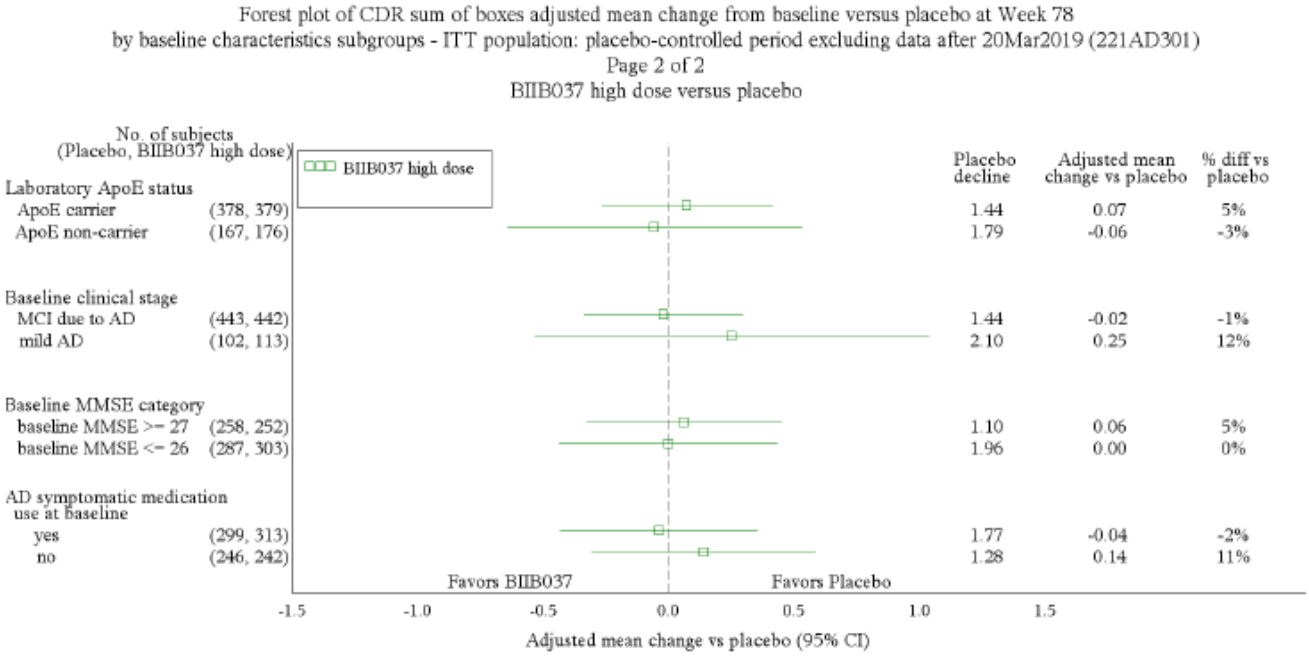
Figure 17: Forest Plot of CDR-SB Adjusted Mean Change From Baseline Versus Placebo at Week 78 by Demographic Subgroups – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change versus placebo and its 95% confidence interval for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with the following fixed effects (excluding covariates defining the subgroup): treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-FOR-SUB-DM-PC.SAS Data as of: 06NOV2019 Run date: 26MAY2020

Figure 18: Forest Plot of CDR-SB Adjusted Mean Change From Baseline Versus Placebo at Week 78 by Baseline Characteristics Subgroups – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019 – High Dose



NOTE: Adjusted mean change versus placebo and its 95% confidence interval for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with the following fixed effects (excluding covariates defining the subgroup): treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. Subjects with undetermined laboratory ApoE status are grouped in the randomized ApoE subgroup.

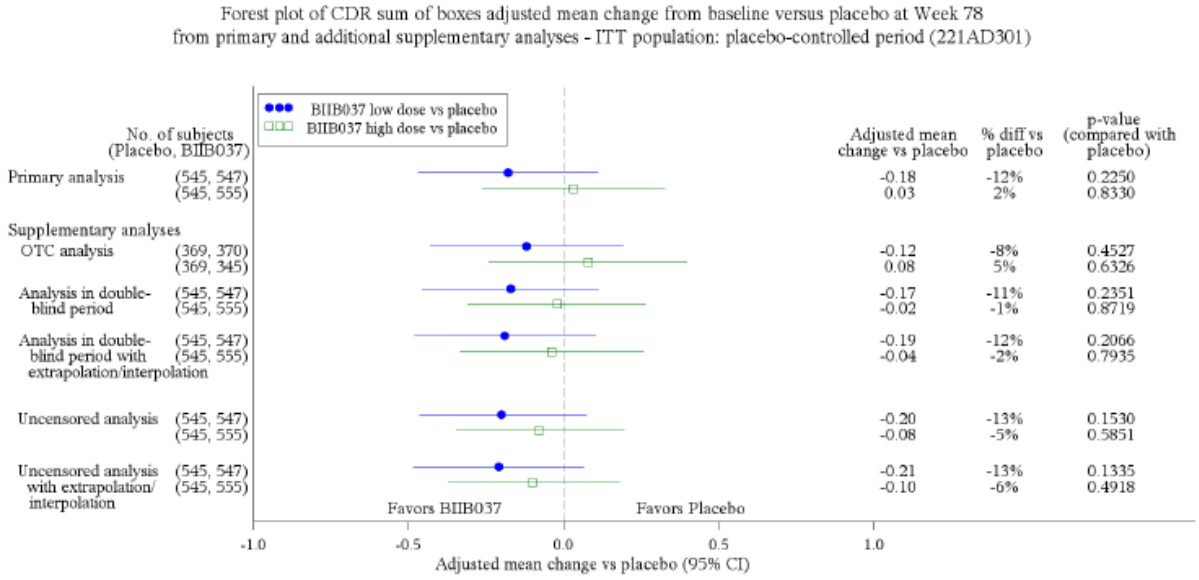
SOURCE: BIIB037AD/221AD301/CSR/F-EF-FOR-SUB-BL-PC.SAS Data as of: 06NOV2019 Run date: 07APR2020

Sensitivity analyses

The results of supplementary analyses for the ITT Population during the double-blind period, the ITT Population with uncensored data, and the Opportunity-to-Complete Population were similar to the primary analysis (Figure 19). In these analyses, a smaller percentage of missing data was expected by either restricting to participants who had the opportunity to complete the study before the futility announcement or including data collected after futility announcement.

The censoring after intercurrent events and per-protocol analyses evaluated the treatment effect under good protocol compliance, such as no treatment discontinuation or medication change or violations of major inclusion criteria, etc. The results of these analyses (Figure 20) were consistent with the primary analysis. All p-values presented are nominal.

Figure 19: Forest Plot of CDR-SB Adjusted Mean Change from Baseline Versus Placebo at Week 78 From Primary and Additional Supplementary Analyses – ITT Population: Placebo-Controlled Period

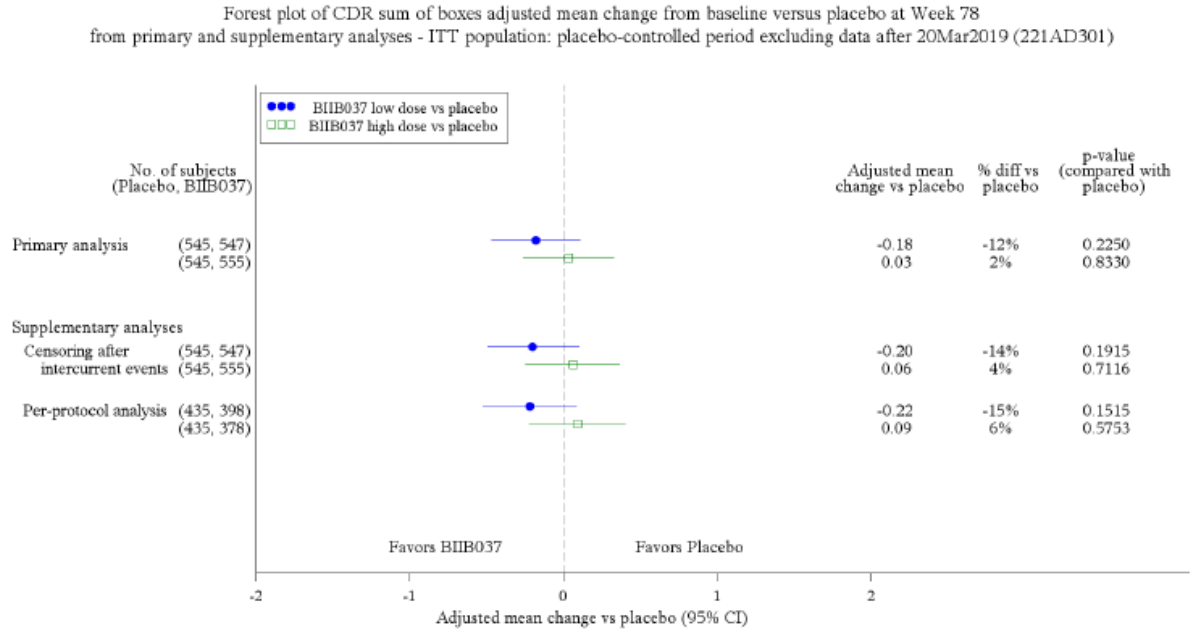


NOTE 1: The primary and supplementary analyses were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
NOTE 2: The primary and OTC analyses excluded data after 20Mar2019. The analysis in double-blind period and the analysis in double-blind period with extrapolation/interpolation excluded data after 17Apr2019. The uncensored analysis and the uncensored analysis with extrapolation/interpolation used all data.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-FOR-ADD-PC.SAS

Data as of: 06NOV2019 Run date: 08APR2020

Figure 20: Forest Plot of CDR-SB Adjusted Mean Change From Baseline Versus Placebo at Week 78 From Primary and Supplementary Analyses – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: The primary and supplementary analyses were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

SOURCE: BIIB037AD/221AD301/CSR/F-EF-FOR-PC.SAS

Data as of: 06NOV2019 Run date: 08APR2020

Post-hoc analyses

The applicant explored reasons why Study 301 did not meet its endpoints (in contrast to Study 302, see below) by conducting several **post-hoc analyses**. These analyses lack pre-specification and control for multiplicity, and are exploratory in nature. Furthermore, specific concerns exist with several of these analyses, as detailed below.

In addition, the Applicant has conducted several analyses comparing Study 301 and Study 302, those are presented in this report after the results of Study 302.

Removal of rapid progressors

Rapidly progressive Alzheimer's disease patients are found in clinical practice and have been described in the literature.

Using a change from baseline to Week 78 of >8 on the CDR-SB, which is 4-fold the upper range of the typical decline, 31 of the 3285 randomised participants (<1%) participants in the 2 studies combined were identified as rapid progressors. The Applicant retrospectively investigated whether baseline characteristics or post-baseline events (e.g. ARIA) could explain such progression, but did not identify any clear unifying cause.

Of the 31 rapid progressors, 18 were in Study 301, with 4 in the Placebo arm, 5 in the Low Dose Arm, and 9 in the High dose arm. Under the assumption that those would have been rapid progressors regardless the treatment assignment, and under the understanding that few outliers could influence average values, the Applicant has performed analyses that exclude patients with a progression of > 8 on the CDR-SB for the primary and secondary endpoints (Table 16), and explored different cut-offs for the primary endpoint (Table 17).

Table 16: Primary and main secondary clinical endpoints of Study 301 while considering the whole population (right) or when excluding patients progressing more than 8 points on the CDR-SB (left).

	Study 301 – excl. CDR-SB change>8			Study 301 – ITT		
	Placebo decline (N=541)	diff vs. placebo (%) [a] p-value		Placebo decline (N=545)	diff vs. placebo (%) [a] p-value	
		Low dose (N=542)	High dose (N=546)		Low dose (N=547)	High dose (N=555)
CDR-SB	1.47	-0.19 (-13%) 0.1430	-0.09 (-6%) 0.5073	1.56	-0.18 (-12%) 0.2250	0.03 (2%) 0.8330
MMSE	-3.5	0.2 (-6%) 0.3837	0.1 (-3%) 0.7646	-3.5	0.2 (-6%) 0.4795	-0.1 (3%) 0.8106
ADAS-Cog 13	5.033	-0.607 (-12%) 0.2223	-0.818 (-16%) 0.1072	5.140	-0.583 (-11%) 0.2536	-0.588 (-11%) 0.2578
ADCS-ADL-MCI	-3.7	0.8 (-22%) 0.0625	1.0 (-27%) 0.0248	-3.8	0.7 (-18%) 0.1225	0.7 (-18%) 0.1506

Table 17: Primary endpoint on of Study excluding rapid progressors according to different definitions

	Study 301		
		Difference From Placebo, % (p-value)	
Cut-off	Placebo Decline	Low Dose	High Dose
>6	1.35	-0.16, -12% (0.1848)	-0.09, -7% (0.4329)
>7	1.42	-0.15, -11% (0.2384)	-0.05, -4% (0.6778)
>8	1.47	-0.19, -13% (0.1430)	-0.09, -6% (0.5073)
>9	1.52	-0.19, -13% (0.1573)	-0.05, -3% (0.7104)
>10	1.56	-0.20, -13% (0.1681)	-0.05, -3% (0.7468)

It is observed that none of the cut-offs would change the conclusion of lack of effect, as demonstrated on the primary endpoint. Furthermore, excluding patients based on observed outcome leads to non-interpretable results, not only as it violated the randomisation but also as it cannot be excluded that progression is dependent on treatment assignment.

Focus on patients treated according to the paradigm in place from Protocol Version 4 on

As discussed above, the study underwent several protocol amendments. Several of the changes implied exposure to higher doses, especially for APOE ε4 carriers or patients who encountered ARIA events. The Applicant presented an analysis focusing on the "PV4" dataset (see definition above), reported in Table 18.

Table 18: Results by Protocol Version 4 status

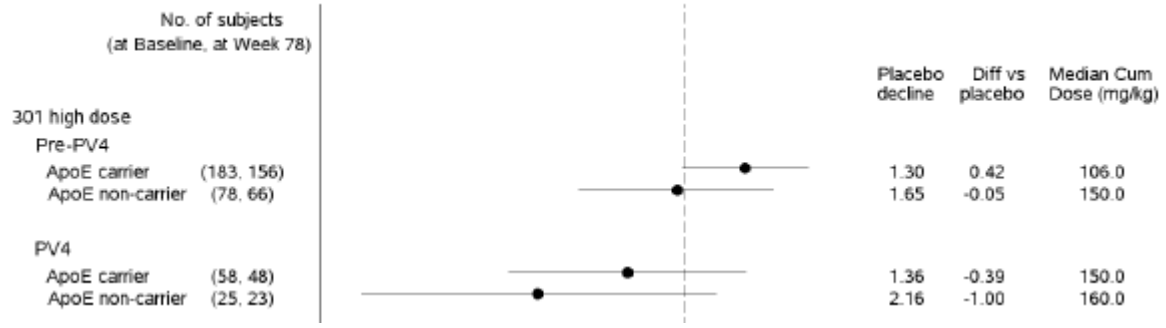
	PV4 Subgroup (censored after 20Mar2019)			PV4 Subgroup (uncensored)		
	Placebo decline	Diff vs pbo* (%) CI	Diff vs pbo* (%) CI	Placebo decline	Diff vs pbo* (%) CI	Diff vs pbo* (%) CI
	N=251	Low dose N=270	High dose N=288	N=25	Low dose N=270	High dose N=288
CDR-SB	1.84	-0.42 (-23%) (-0.940, 0.101)	-0.49 (-27%) (-1.016, 0.045)	1.78	-0.31 (-17%) (-0.710, 0.097)	-0.46 (-26%) (-0.854, -0.057)
MMSE	-3.8	0.9 (-24%) (-0.02, 1.90)	0.5 (-13%) (-0.44, 1.53)	-4.0	0.8 (-20%) (0.09, 1.59)	1.0 (-25%) (0.22, 1.71)
ADAS -Cog 13	4.849	-0.136 (-3%) (-1.9301, 1.6579)	-0.977 (-20%) (-2.8269, 0.8735)	4.688	-0.024 (-1%) (-1.3174, 1.2684)	-0.757 (-16%) (-2.0444, 0.5314)
ADCS -ADL-MCI	-5.0	1.5 (-30%) (-0.23, 3.19)	3.0 (-60%) (1.24, 4.75)	-4.4	1.1 (-25%) (-0.13, 2.43)	2.3 (-52%) (1.06, 3.59)

It is observed that the results are still modest and inconsistent across endpoints, and only significant on the primary endpoint when the uncensored dataset is used.

It is also observed (see

Figure **21** below) that while the main change in dosing (attributable to changes in the protocol) is in ApoE carriers, the results are different for both carriers and non-carriers.

Figure 21: Forest plot of the results of the high-dose arm of Study 301 by protocol version and ApoE status.



If the PV4 really defines a new hypothesis, this has to be tested prospectively and the results above are just exploratory.

Furthermore, the same pattern is not observed in Study 302 (see below).

Results – Study 302

In line with the *Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design*, the main results presented will relate to the final analysis (i.e. the analysis including overrunning patients). However, given the discordance between the interim analysis and the final analysis, the results with the interim dataset for the primary analysis will also be briefly reported and – in line with the reflection paper mentioned above – will also be taken into account.

Participant flow – Study 302

Planned: 1605 patients.

Randomized: 1643 patients were randomized (549 patients to placebo, 547 patients to aducanumab low dose and 547 to aducanumab high dose) and 1638 were dosed.

Completed: 874 (53.4%) patients completed the study (288 (52.6%) patients on placebo and 291 (53.6%) patients on aducanumab low dose and 295 (53.9%) on aducanumab high dose).

Date first patient dosed: 15 September 2015

Date last patient dosed: 20 March 2019

Date last safety follow-up visit: 5 August 2019

Europe/Canada was the region where the largest number of patients were randomized and dosed (52.8%), followed by the US (39.8%) and Asia (7.4%). Japan was the only country in Asia that enrolled patients.

Data on screening failures were provided upon request. In total, there were 4114 screening failures. The Applicant explained that the majority of screening failures (n=3210, 62.8%) was because patients did not meet the clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria, or did not meet the requirements of the cognitive screenings outcomes. In addition, 17.7% (n=903) of screening failures

were patients with a negative PET scan. In 3.4% (n= 173) of cases, the reason for exclusion was brain MRI findings at screening.

Slightly more than half of the randomized patients completed the study. The most common reason for discontinuation/withdrawal from the study was 'other'. This coding was, in the majority of cases, indicating the non-completion due to termination of the study. The second most reason for not completing the study was 'adverse event'. This was the case for 3.1% of placebo, 7.7% of the low-dose and 9.0% of the high-dose. A small number of patients discontinued because of disease progression. 27.8% Of the major protocol violation concerned the inform consent.

Since the high dose for ApoE ε4 carriers was amended, only 9% of the ApoE ε4 carriers received all 14 doses of 10 mg/kg. On the other hand, a total of 37.2% of ApoE ε4 noncarriers received all 10 mg/kg doses.

Baseline data – Study 302

As in Study 301, the included study population is considered representative for the target population of MIC due to AD and mild AD, in population and clinical characteristics. There were no relevant differences between treatment groups regarding demographics and baseline disease characteristics, see Table 19 and Table 20. Slightly over 2/3 of patients were APOE ε4 carriers, the main known genetic risk factor of AD. This is in line with the percentage of APOE ε4 carriers in confirmed AD.

In total, 51.8% of the patients used cholinesterase inhibitors or memantine at baseline. Moreover, 14.6% of the patients stopped symptomatic AD treatment prior to entering the study.

Table 19: Participant Demographics and Baseline Characteristics—Final Dataset, ITT Population—Study 302 (symptomatic AD medication added by the assessor)

	Placebo (N=548)	Low dose (N=543)	High dose (N=547)	Total (N=1638)
Age in years, mean ± SD	70.8±7.40	70.6±7.45	70.6±7.47	70.7±7.43
Sex, Female n (%)	290 (52.9)	269 (49.5)	284 (51.9)	843 (51.5)
Race				
Asian n (%)	47 (8.6)	39 (7.2)	42 (7.7)	128 (7.8)
White n (%)	431 (78.6)	432 (79.6)	422 (77.1)	1285 (78.4)
Education years, mean ± SD	14.5±3.68	14.5±3.63	14.5±3.60	14.5±3.63
AD medications used, n (%)	282 (51.5)	281 (51.7)	285 (52.1)	848 (51.8)
ApoE ε4, n (%)				
Carriers	368 (67.2)	362 (66.7)	365 (66.7)	1095 (66.8)
Homozygote ε4	92 (16.8)	97 (17.9)	77 (14.1)	266 (16.2)
Heterozygote ε4	276 (50.4)	265 (48.8)	288 (52.7)	829 (50.6)

Non-carriers	178 (32.5)	178 (32.8)	181 (33.1)	537 (32.8)
Clinical stage, n (%)				
MCI due to AD	446 (81.4)	452 (83.2)	438 (80.1)	1336 (81.6)
Mild AD	102 (18.6)	91 (16.8)	109 (19.9)	302 (18.4)
(n) - PET substudy	(159)	(159)	(170)	(488)
PET SUVR, mean composite ± SD	1.375±0.1748	1.394±0.1837	1.383±0.1833	1.384±0.1805
Symptomatic AD medication, n (%)	282 (51.5)	281 (51.7)	285 (52.1)	848 (51.8)
Cholinesterase inhibitors, n (%)	235 (42.9)	230 (42.4)	228 (41.7)	693 (42.3)
Memantine, n (%)	8 (1.5)	15 (2.8)	21 (3.8)	44 (2.7)
Both, n (%)	39 (7.1)	36 (6.6)	36 (6.6)	111 (6.8)
AD medication stopped at entry, n (%)	90 (16.4)	80 (14.7)	81 (14.8)	251 (15.3)

AD = Alzheimer's disease; ApoE ε4 = apolipoprotein E ε4; ITT = intent-to-treat; MCI = mild cognitive impairment; n = number; PET = positron emission tomography; SD = standard deviation

Data source: Appendix G1 Table 2, Table 3, Table 4, and Table 5, CSR Study 302

Table 20: Baseline Clinical Scores—Final Dataset, ITT Population—Study 302

	Placebo (N=548)	**Low dose (N=543**	**High dose (N=547)**	**Total (N=1638)**
RBANS delayed memory score, mean ± SD	60.5±14.23	60.0±14.02	60.7±14.15	60.4±14.13
MMSE, mean ± SD	26.4±1.78	26.3±1.72	26.3±1.68	26.3±1.73
CDR Global Score, n (%)				
0.5	545 (99.5)	543(100)	546 (99.8)	1634 (99.8)
1	3 (0.5)	0	1 (0.2)	4 (0.2)
CDR-SB, mean ± SD	2.47±0.999	2.46±1.011	2.51±1.053	2.48±1.021
CDR cognitive subscore, mean ± SD	1.75±0.644	1.76±0.643	1.78±0.650	1.76±0.646
CDR functional subscore, mean ± SD	0.72±0.555	0.71±0.558	0.73±0.577	0.72±0.563

ADAS-Cog 13, mean ± SD	21.9±6.73	22.5±6.76	22.2±7.07	22.2±6.86
ADCS-ADL-MCI score, mean ± SD	42.6±5.73	42.8±5.48	42.5±5.82	42.6±5.68

ADAS-Cog 13 =Alzheimer's Disease Assessment Scale – Cognitive Subscale (13 items); ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR-SB = Clinical Dementia Rating – Sum of Boxes; ITT = intent-to-treat; MMSE = Mini-Mental State Examination; PBO = placebo; n = number; RBANS = Repeatable Battery for Neuropsychological Status

Data source: Appendix G1 Table 4

488 patients participated in the PET sub-study: 159 on placebo, 159 on the low dose and 170 on the high dose. There were no relevant differences between treatment groups in the PET sub-study regarding demographics and baseline disease characteristics. This subsample appears a good reflection of the main study population.

Numbers analysed – Study 302

Please refer to Table 7 above for numbers analysed.

Outcomes and estimation – Study 302

Primary endpoint

The primary endpoint was Change from Baseline in CDR-SB at Week 78. The difference in change from baseline in CDR-SB at Week 78 between aducanumab high-dose and placebo was -0.39 (-22% compared to placebo), p = 0.0120. The difference in change from baseline in CDR-SB at Week 78 between aducanumab low-dose and placebo was -0.26 (-15% compared to placebo, p=0.0901), see Table 21 and Figure 22.

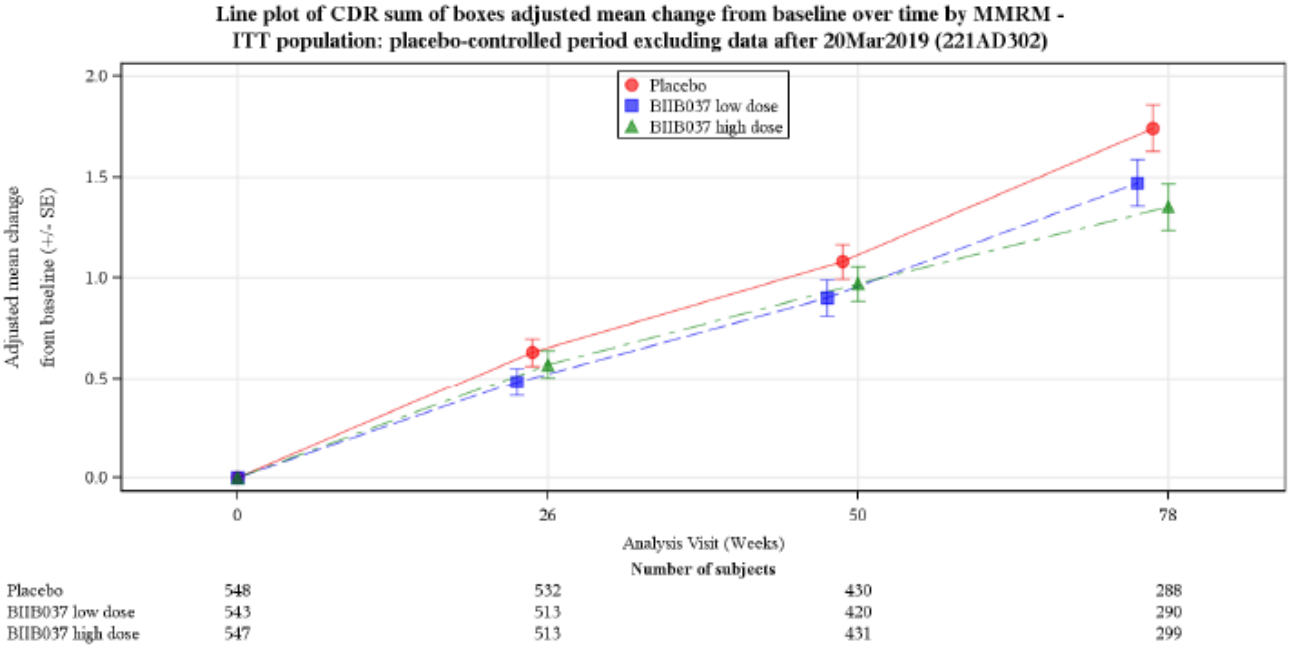
Table 21: Change from Baseline in CDR-SB at Week 78: Study 302, ITT Censored Analysis

	Placebo (N=548)	**Low dose** (N=543)	**High dose** (N=547)
CDR-SB Baseline (mean±SD)	2.47±0.99	2.46±1.011	2.51±1.053
CDR-SB at week 78 (mean±SD)	4.22±2.308	3.88±2.397	3.76±2.382
Change on CDR-SB at week 78 (adjusted mean±se)	1.74±0.12	1.47±0.12	1.35±0.12
Difference versus placebo at week 78 (%)		-0.26 (-15%)	-0.39 (-22%)
Confidence interval for difference		-0.57;0.04	-0.694;-0.086
p-value		0.0901	0.0120

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction,

baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 22: Line Plot of CDR-SB Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD302/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 25NOV2019

On the other hand, using the dataset used for the futility analysis (i.e. without overrunning patients) the estimated difference between High Dose and Placebo is -0.28, while the difference between Low Dose and placebo is -0.1. For both arms, the conditional power was below threshold.

Domain Analysis of CDR

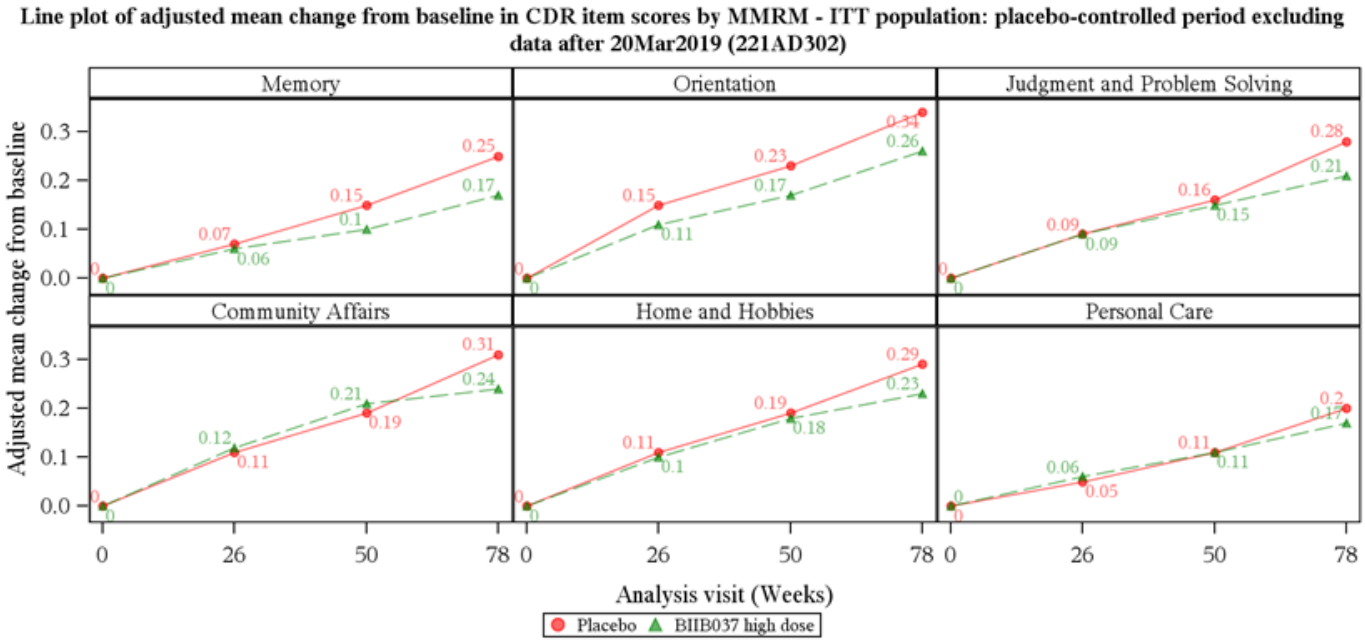
The difference between the aducanumab high-dose group and the placebo group based on the change from baseline on the CDR **cognitive** subscore at Week 78 was -0.23 (-26% compared to placebo, p=0.0052). The difference between the aducanumab low-dose group and the placebo group was -0.17 (-19% compared to placebo, p=0.0398).

The difference between the aducanumab high-dose group and the placebo group based on the change from baseline on the CDR **functional** subscore at Week 78 was -0.16 (-20% compared to placebo, p=0.0826). The difference between the aducanumab low-dose group and the placebo group was -0.10 (-12% compared to placebo, p=0.2555).

Figure **23** displays the adjusted mean change from baseline on the six CDR domains.

Higher proportions of patients in the high-dose (70.2%) and low-dose (63.8%) groups had a global CDR-score of 0.5 at the Week 78 visit compared to patients in the placebo group (58.7%). This means that these patients showed no progression on this global score since a global CDR-score of 0.5 was required for study inclusion.

Figure 23: Line Plot of Adjusted Mean Change from Baseline in CDR Items Scores by MMRM – ITT Population: Placebo-Controlled Period Excluding Data after 20Mar2019 (221AD302)



NOTE: Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline item value, baseline item score by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region and laboratory ApoE status. All three treatment groups were included in the model.

SOURCE: BIIB037AD/EMA/MAA/F-CDR-ITEM-LINE-MMRM-PC-302.SAS Data as of: 06NOV2019 Run date: 17AUG2020

Secondary endpoints

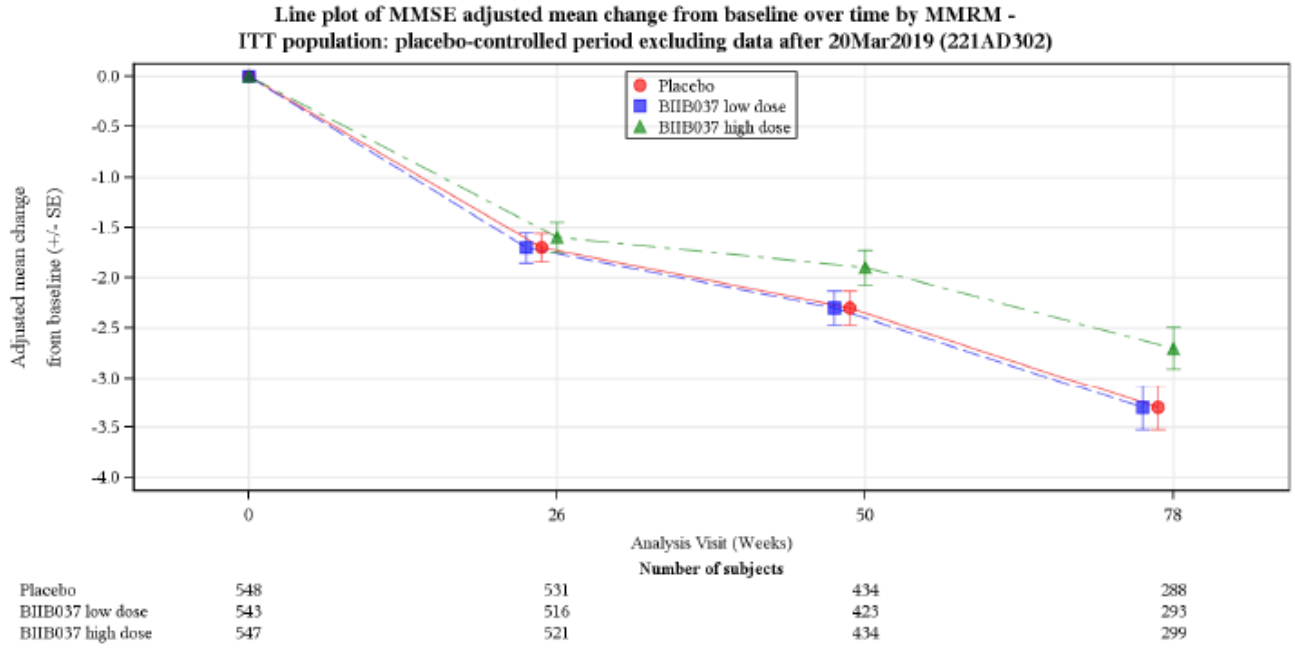
According to the type I error control strategy applied, after a statistically significant test of the primary endpoint for high dose compared to placebo, full alpha is propagated to both the primary endpoint comparison for low dose and to the first secondary endpoint comparison for high dose. In view of this, the Applicant claims that the results of the secondary endpoints have full inferential validity. However, the strategy does not control the study-wise type I error rate at 0.05. Indeed, the Applicant itself indicates this only controls the study-wise type I error rate between 0.05 and 0.1. Hence, the results on the secondary endpoint should be interpreted with caution. Regardless of the strictly inferential evaluation, the results on the secondary endpoints (Tables 22-24 and Figures 24-26) are generally supportive.

Table 22: Change from Baseline in MMSE at Week 78: Study 302, ITT Censored Analysis (made by the assessor)

	Placebo (N=548)	Low dose (N=543)	High dose (N=547)
MMSE Baseline (mean±SD)	26.4±1.78	26.3±1.72	26.3±1.68
MMSE at week 78 (mean±SD)	23.1±3.54	22.9±4.57	23.6±4.21
Change on MMSE at week 78 (adjusted mean±se)	-3.3±0.22	-3.3±0.22	-2.7±0.21
Difference versus placebo at week 78 (%)		-0.1 (3%)	0.6 (-18%)
Confidence interval for difference		-0.65;0.48	0.00;1.13
Nominal p-value		0.7578	0.0493

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 24: Line Plot of MMSE Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in MMSE as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline MMSE value, baseline MMSE by visit interaction, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD302/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 25NOV2019

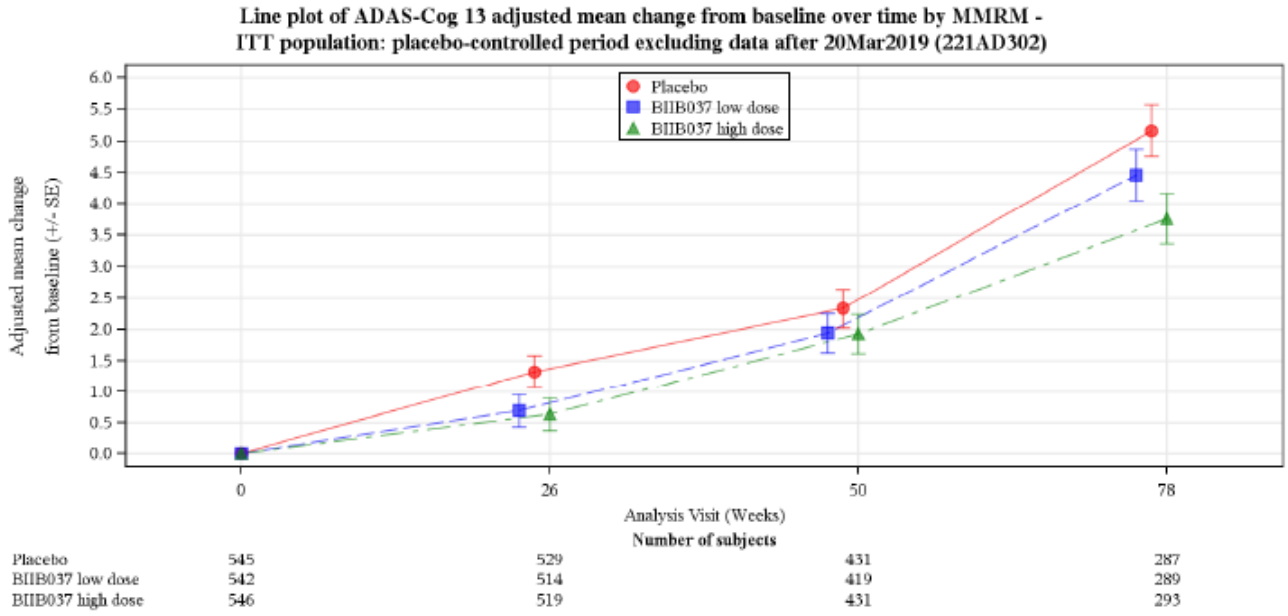
Change from baseline in ADAS-Cog13 score at Week 78

Table 23: Change from Baseline in ADAS-Cog13 at Week 78: Study 302, ITT Censored Analysis (made by the assessor)

	Placebo (N=548)	Low dose (N=543)	High dose (N=547)
ADAS-COG Baseline (mean±SD)	21.9±6.72	22.5±6.76	22.3±7.07
ADAS-COG at week 78 (mean±SD)	27.1±10.03	26.94±10.44	25.97±9.39
Change on ADAS-COG at week 78 (adjusted mean±se)	5.16±0.40	4.46±0.41	3.76±0.40
Difference versus placebo at week 78 (%)		-0.70 (-14%)	-1.4 (-27%)
Confidence interval for difference		-1.76;0.36	-2.46;-0.34
Nominal p-value		0.1962	0.0097

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 25: Line Plot of ADAS-Cog13 Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in ADAS-Cog 13 as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline ADAS-Cog 13, baseline ADAS-Cog 13 by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD302/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 25NOV2019

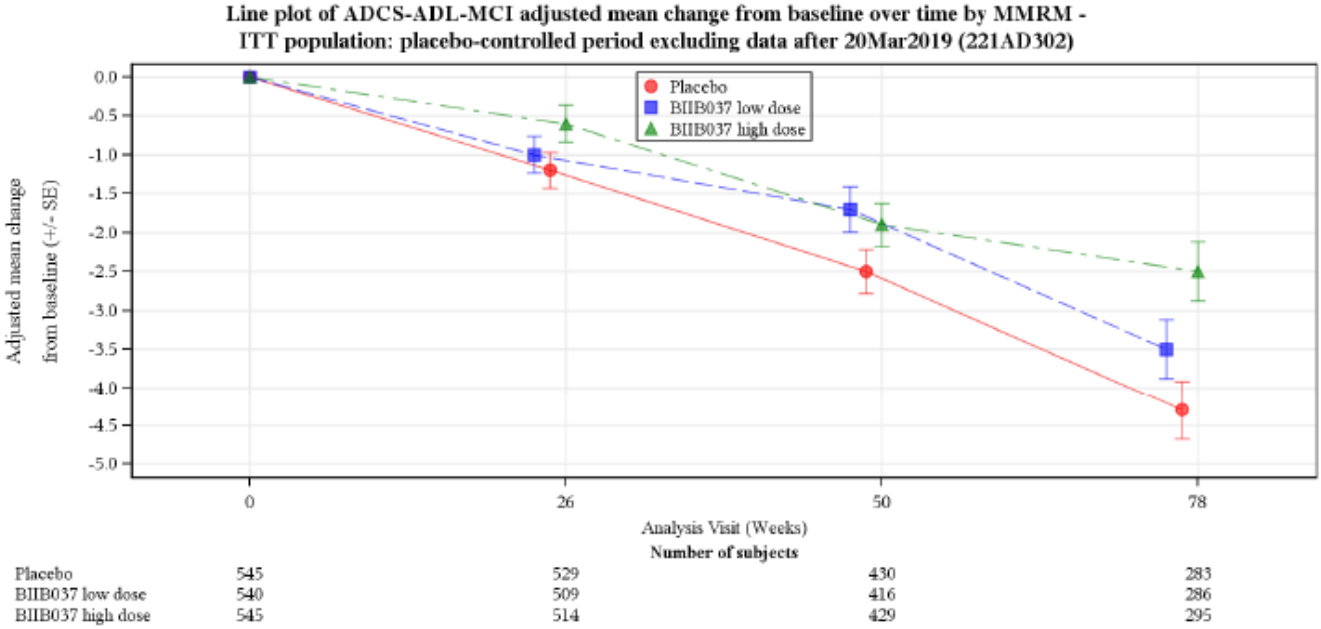
Change from baseline in ADCS-ADL-MCI score at Week 78

Table 24: Change from Baseline in ADCS-ALD-MCI at Week 78: Study 302, ITT Censored Analysis (made by the assessor)

	Placebo (N=548)	Low dose (N=543)	High dose (N=547)
ADCS-ADL-MCI Baseline (mean±SD)	42.6±5.73	42.8±5.48	42.5±5.82
ADCS-ADL-MCI at week 78 (mean±SD)	38.5±8.40	39.9±8.02	40.5±7.67
Change on ADCS-ADL-MCI at week 78 (adjusted mean±se)	-4.3±0.38	-3.5±0.38	-2.5±0.38
Difference versus placebo at week 78 (%)		0.7 (-16%)	1.7 (-40%)
Confidence interval for difference		-0.27;1.73	0.75;2.74
Nominal p-value		0.1515	0.0006

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Figure 26: Line Plot of ADCS-ADL-MCI Adjusted Mean Change From Baseline Over Time by MMRM – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in ADCS-ADL-MCI as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline ADCS-ADL-MCI, baseline ADCS-ADL-MCI by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.
Abbreviations: SE = standard error.

SOURCE: BIIB037AD/221AD302/CSR/F-EF-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 25NOV2019

Most important tertiary endpoints

NPI-10

Table 25: Change from Baseline in NPI-10 at Week 78: Study 302, ITT Censored Analysis (made by the assessor)

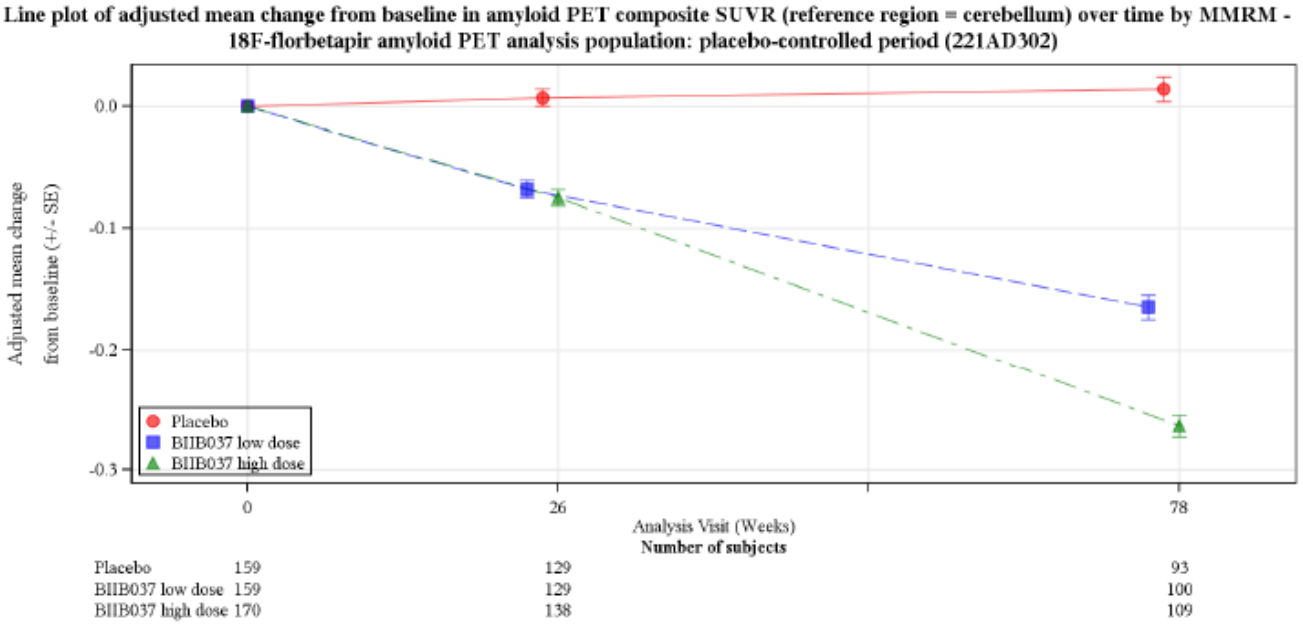
	Placebo (N=548)	**Low dose** (N=543)	**High dose** (N=547)
NPI-10 Baseline (mean±SD)	4.3±5.90	4.1±6.19	4.5±6.38
NPI-10 at week 78 (mean±SD)	6.4±8.99	5.4±7.92	5.4±7.68
Change on NPI-10 at week 78 (adjusted mean±se)	1.5±0.43	1.0±0.44	0.2±0.43
Difference versus placebo at week 78 (%)		-0.5 (-33%)	-1.3 (-87%)
Confidence interval for difference		-1.62;0.64	-2.45;-0.20
p-value		0.3921	0.0215

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDRSB as dependent variable and with fixed effects of treatment group, categorical visit, treatment by visit interaction, baseline CDRSB, baseline CDRSB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

Change from baseline in Aβ PET signal

The adjusted mean change from baseline in Aβ PET composite SUVR relative to placebo was in favour of aducanumab at both dose levels at Week 26 (high-dose, -0.082 [p<0.0001]; low-dose, -0.075 [p<0.0001]) and Week 78 (high-dose, -0.278 [p<0.0001]; low-dose, -0.179 [p<0.0001]), see Figure 27. These results indicate that a higher dose level and longer treatment duration was associated with a greater reduction in Aβ plaque levels as measured by Aβ PET. Due to the similarity of dosing during the titration phase, a separation between the low and the high-dose groups at Week 26 was expected to be minimal.

Figure 27: Line Plot of Adjusted Mean Change From Baseline in Amyloid PET Composite SUVR Reference Region = Cerebellum) Over Time by MMRM – 18F-florbetapir Amyloid PET Analysis Population: Placebo-Controlled Period



NOTE: Adjusted mean change and standard error for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in SUVR as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR value, baseline SUVR value by visit interaction, baseline MMSE, baseline age and laboratory ApoE status.

SOURCE: BIIB037AD/221AD302/CSR/F-PET-LIN-MMRM-PC.SAS Data as of: 06NOV2019 Run date: 22NOV2019

Correlation of Aβ and primary endpoint

A negligible correlation between change in cerebral amyloid beta load and change in the primary endpoint was found, see Table 26.

Table 26: Correlation and partial correlation for change from baseline amyloid PET composite SUVR (reference region = cerebellum) versus change from baseline CDR sum of boxes at Week 78 – 18F-florbetapir amyloid PET analysis population: placebo-controlled period excluding efficacy data after 20Mar2019 (Study 302), made by the assessor

	Placebo	Aducanumab low dose	Aducanumab high dose	Total
N evaluable for correlation analysis	84 (52.8)	88 (55.3)	97 (57.1)	185 (56.2)
Pearson correlation **95% CI** **p-value**	-0.01 (-0.224, 0.205) 0.9268	0.16 (-0.047, 0.362) 0.1258	-0.04 (-0.235, 0.164) 0.7210	0.11 (-0.039, 0.246) 0.1528
Spearman correlation **95% CI** **p-value**	-0.05 (-0.259, 0.169) 0.6713	0.22 (0.013, 0.412) 0.0375	0.00 (-0.200, 0.199) 0.9993	0.13 (-0.013, 0.271) 0.074

Partial Pearson correlation **95% CI** **p-value**	0.00 (-0.214, 0.220) 0.9755	0.15 (-0.064, 0.350) 0.1701	0.10 (-0.101, 0.298) 0.3233	0.17 (0.022, 0.305) 0.0238
Partial Spearman correlation **95% CI** **p-value**	-0.06 (-0.271, 0.161) 0.6071	0.19 (-0.026, 0.383) 0.0855	0.13 (-0.077, 0.320) 0.2233	0.19 (0.048, 0.327) 0.0093

NOTE: Partial correlations are calculated adjusting for baseline amyloid PET SUVR and baseline CDR sum of boxes.

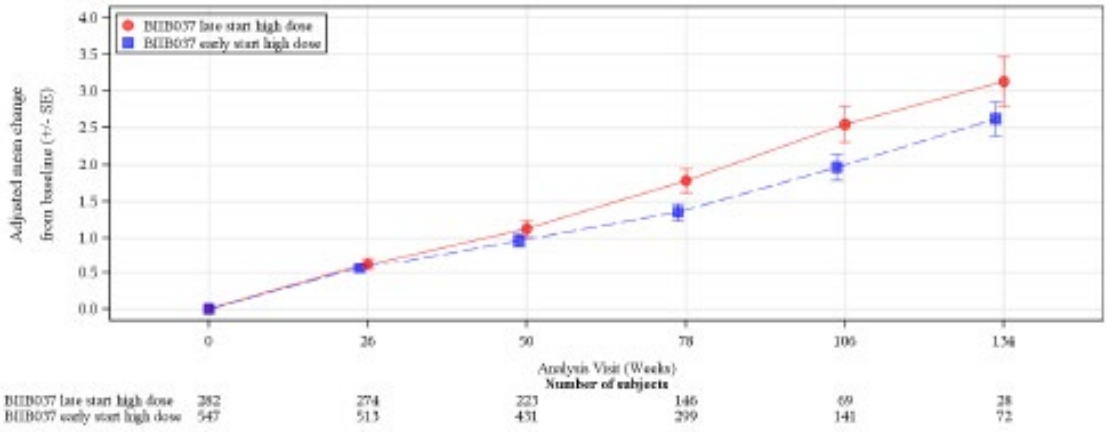
Long-term extension

After the completion of the placebo-controlled period, 263 Patients on placebo, 251 on an aducanumab low dose and 257 on aducanumab high dose rolled over into the LTE (N=771, 47.1% of total patients randomized in the placebo-controlled period). During the LTE period, participants who were randomized to aducanumab (low-dose or high-dose) in the PC period continued to receive aducanumab on the same dose (‘*early start, remained on aducanumab’*) and participants who were randomized to placebo during the PC period were switched to receive aducanumab (high-dose or low-dose as randomized at study entry; ‘*late start*’, ‘*placebo → aducanumab’*).

Since the study terminated early, data up to 56 weeks -with small numbers of patients- in addition to the 78 weeks RCT are available instead of data for up to 5 years. This limits the possibility to adequately assess the long-term effects of the treatment with aducanumab.

On the CDR-SB, the differences in change from baseline between the ‘remained on aducanumab’ high-dose group compared to the ‘placebo → aducanumab’ high-dose group seems to remain stable over time (see Figure 28 below). However, the short duration and the very small numbers lower the credibility of this finding.

Figure 28: Line plot of CDR-SB, placebo-controlled and LTE of Study 302.

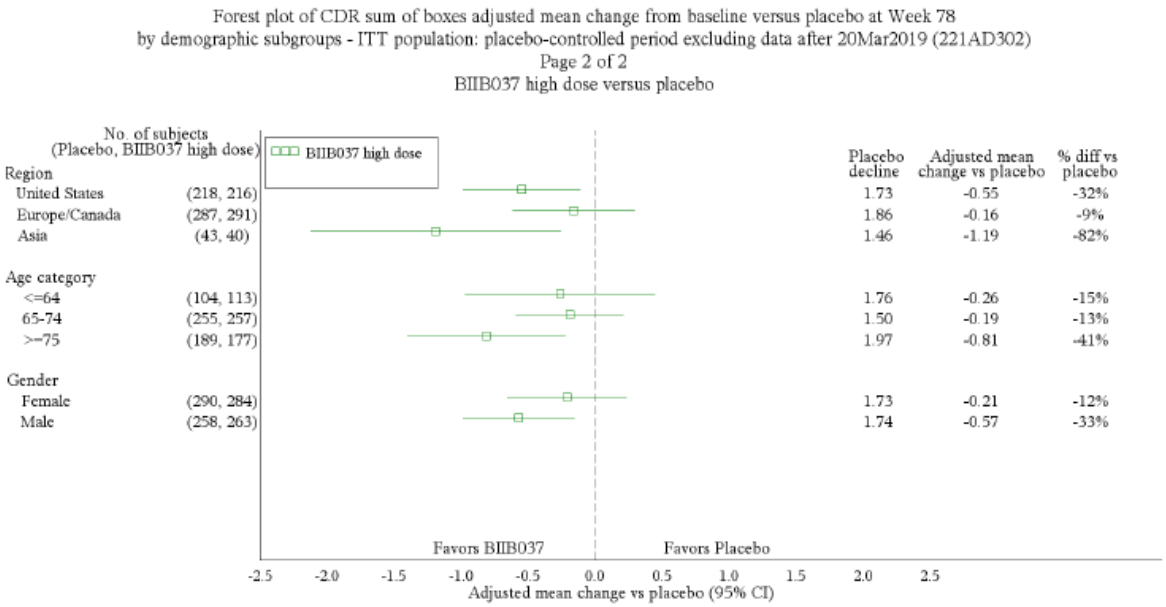


In general, on the secondary endpoints the same pattern was observed, except for the MMSE, were the ‘placebo → aducanumab’ high dose seem to progress faster after switching to aducanumab, than when they were on placebo.

Ancillary analyses – Study 302

Figure 29 and Figure 30 show forest plots of the primary endpoint for subgroups according to demographic and baseline characteristics. Results the subgroup are irregular and appear at random. For Study 301 a mirrored patchy pattern was seen. Thus, there is no consistency in subgroup analyses between Study 301 and 302. The results are compatible with random variability, with no subgroup that could be identified as potentially as benefitting more from treatment.

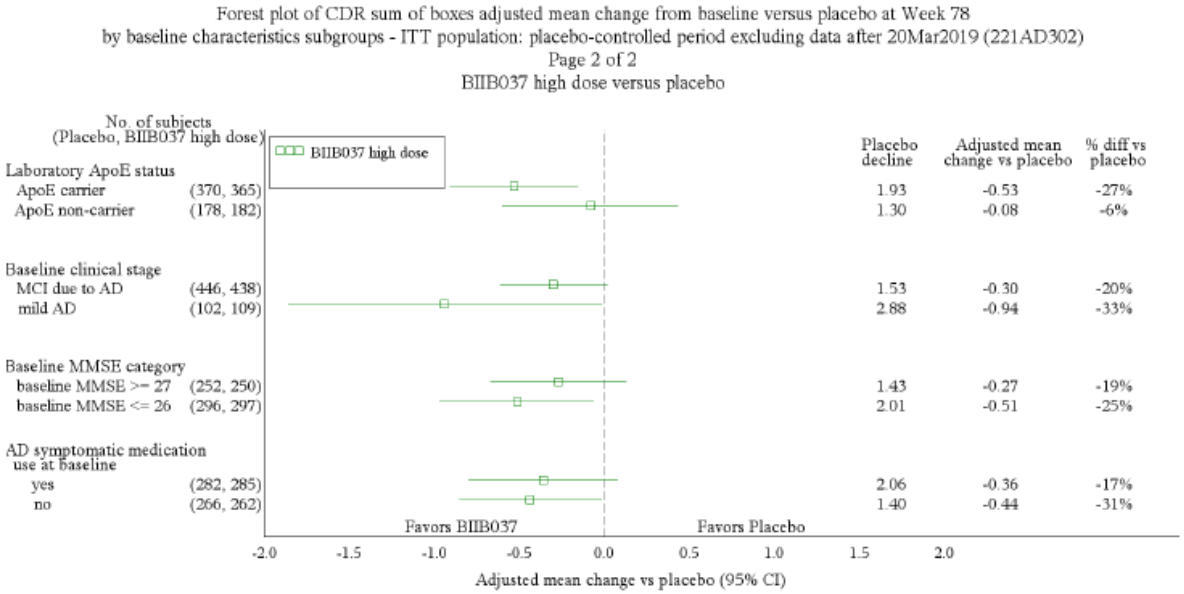
Figure 29: Forest Plot of CDR-SB Adjusted Mean Change From Baseline Versus Placebo at Week 78 by Demographic Characteristics Subgroups – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019 – High Dose



NOTE: Adjusted mean change versus placebo and its 95% confidence interval for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with the following fixed effects (excluding covariates defining the subgroup): treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

SOURCE: BIIB037AD/221AD302/CSR/F-EF-FOR-SUB-DM-PC.SAS Data as of: 06NOV2019 Run date: 07APR2020

Figure 30: Forest Plot of CDR-SB Adjusted Mean Change From Baseline Versus Placebo at Week 78 by Baseline Characteristics Subgroups – ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019 – High Dose



NOTE: Adjusted mean change versus placebo and its 95% confidence interval for each treatment group were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with the following fixed effects (excluding covariates defining the subgroup): treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. Subjects with undetermined laboratory ApoE status are grouped in the randomized ApoE subgroup.

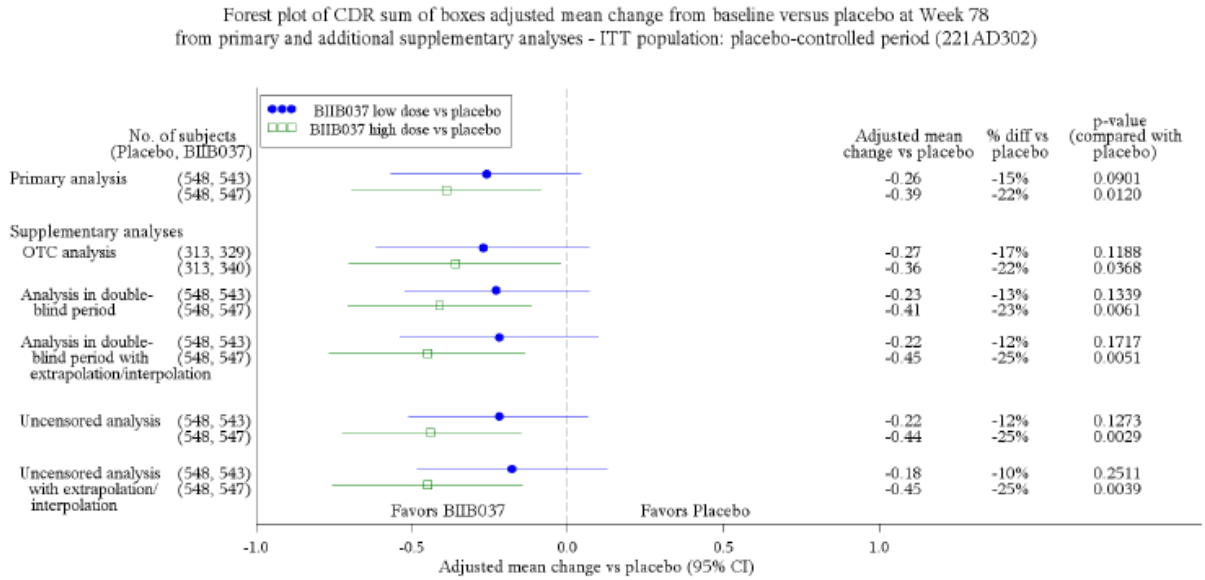
SOURCE: BIIB037AD/221AD302/CSR/F-EF-FOR-SUB-BL-PC.SAS Data as of: 06NOV2019 Run date: 07APR2020

Sensitivity Analyses – Study 302

The results of supplementary analyses for the ITT Population during the double-blind period, the ITT Population with uncensored data, and the Opportunity-to-Complete Population were similar to the primary analysis (Figure 31). In these analyses, a smaller percentage of missing data was expected, by either including data collected after futility announcement or restricting to participants that had the opportunity to complete the study before futility announcement.

The censoring after intercurrent events and per-protocol analyses evaluated the treatment effect under good protocol compliance, such as no treatment discontinuation or medication change or violations of major inclusion criteria, etc. The results of these analyses (Figure 32) were consistent with the primary analysis. All p-values presented are nominal.

Figure 31: Forest Plot of CDR Sum of Boxes Adjusted Mean Change from Baseline Versus Placebo at Week 78 From Primary and Additional Supplementary Analyses - ITT Population: Placebo-Controlled Period



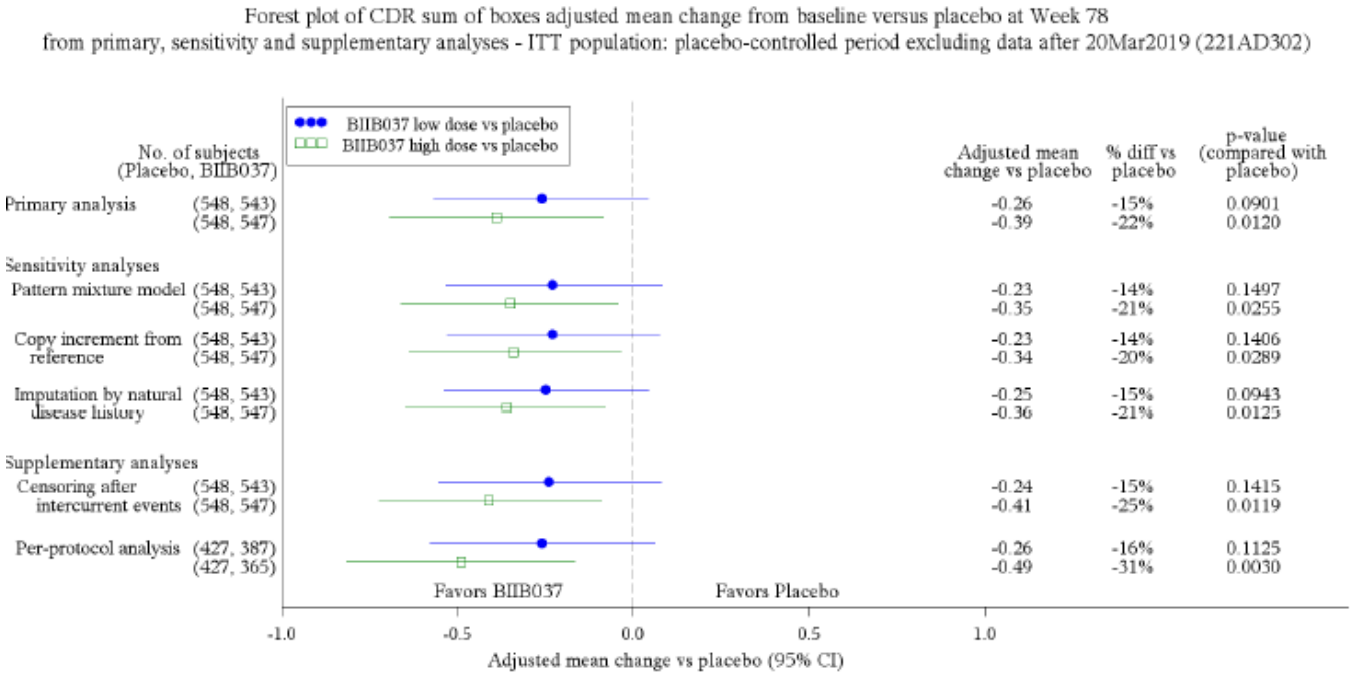
NOTE 1: The primary and supplementary analyses were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

NOTE 2: The primary and OTC analyses excluded data after 20Mar2019. The analysis in double-blind period and the analysis in double-blind period with extrapolation/interpolation excluded data after 17Apr2019. The uncensored analysis and the uncensored analysis with extrapolation/interpolation used all data.

SOURCE: BIIB037AD/221AD302/CSR/F-EF-FOR-ADD-PC.SAS

Data as of: 06NOV2019 Run date: 08APR2020

Figure 32: Forest Plot of CDR-SB Adjusted Mean Change From Baseline Versus Placebo at Week 78 From Primary, Sensitivity, and Supplementary Analyses - ITT Population: Placebo-Controlled Period Excluding Data After 20 March 2019



NOTE 1: The primary and supplementary analyses were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

NOTE 2: The sensitivity analyses were based on an ANCOVA (analysis of covariance) model with change from baseline in CDR-SB as dependent variable and with treatment group, baseline CDR-SB, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status as independent variables.

SOURCE: biib037ad/221ad302/csr/f-cdr-for-pc.sas Data as of: 06NOV2019 Run date: 08APR2020

Furthermore, and in light of the discordant results of Study 301, the Applicant proposed several approaches (both analytical and bootstrap-based) to estimate the probability of the results observed across endpoints in Study 302 (or more extreme favourable results) under a real data-generating mechanism where the treatment does not have any effect on the outcome.

This approach is not supported. Consistency of the primary endpoint with the secondary endpoints cannot be used as argument that Study 302 is not a false positive study. Such consistency is to be expected in both a (true) positive and a false positive study because the primary and secondary endpoints are correlated. The Applicant explained they took into account such correlation; however, the CHMP considers the estimate of the real correlation is not straightforward. Ultimately, the discussion of one false positive and one false negative study cannot be based on an argument built within the positive study only. The concept of "probability of false positive" is overall considered flawed.

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 27: Summary of efficacy for trial 221AD301 (ENGAGE)

Title: A Phase 3 Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease				
Study identifier	Protocol number: 221AD301 EudraCT number: 2015-000966-72 ClinicalTrials.gov identifier (NCT number): NCT02477800			
Design	A multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase 3 study to assess the efficacy and safety of aducanumab in participants with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		78 weeks 8 weeks	
Hypothesis	Superiority			
Treatments groups	High dose		Aducanumab 6 mg/kg after titration over 24 weeks (ApoE ε4 carrier) or 10 mg/kg after titration over 24 weeks (ApoE ε4 noncarrier). This was changed in protocol versions 4-6 into: 10mg/kg after titration over 24 weeks for all patients (regardless of ApoE ε4 status) 78 weeks, n=555 randomised	
	Low dose		Aducanumab 3 mg/kg after titration over 8 weeks (ApoE ε4 carrier) or 6 mg/kg after titration over 24 weeks (ApoE ε4 noncarrier). 78 weeks, n=547 randomised	
	Placebo		78 weeks, n=545 randomised	
Endpoints and definitions	Primary endpoint	CDR-SB	Change from baseline in CDR-SB score at Week 78	
	Secondary endpoints	MMSE	Change from baseline in MMSE score at Week 78	
		ADAS-Cog13	Change from baseline in ADAS-Cog13 score at Week 78	
		ADCS-ADL-MCI	Change from baseline in ADCS-ADL-MCI score at Week 78	
	Tertiary endpoint	NPI-10	Change from baseline in NPI-10 score at Week 78	
Database lock	13 November 2019			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (placebo-controlled period excluding data after 20Mar2019) Week 78			
Descriptive statistics and estimate	Treatment group	Placebo	Low dose	High dose

variability	Number of subject	545	547	555
	CDR-SB (adjusted mean) 95% confidence interval	1.56 (1.344, 1.768)	1.38 (1.164, 1.590)	1.59 (1.370, 1.805)
	MMSE (adjusted mean) 95% confidence interval	-3.5 (-3.94, -3.13)	-3.3 (-3.75, -2.93)	-3.6 (-4.02, -3.19)
	ADAS-Cog13 (adjusted mean) 95% confidence interval	5.140 (4.398, 5.882)	4.558 (3.816, 5.299)	4.552 (3.793, 5.312)
	ADCS-ADL-MCI (adjusted mean) 95% confidence interval	-3.8 (-4.48, -3.12)	-3.1 (-3.76, -2.39)	-3.1 (-3.81, -2.42)
	NPI-10 (adjusted mean) 95% confidence interval	1.2 (0.39, 1.92)	0.1 (-0.65, 0.88)	1.2 (0.43, 2.00)

Effect estimate per comparison	Primary endpoint: Change from baseline in CDR-SB at Week 78	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	-0.18 (-12%)
		95% confidence interval	-0.47;0.11
		P-value	0.2250
		Comparison groups	*High dose vs Placebo*
		Difference from placebo (%)	0.03 (2%)
		95% confidence interval	-0.26;0.33
		p-value	0.8330
	Secondary endpoints: MMSE	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	0.2 (-6%)
		95% confidence interval	-0.35;0.74
		p-value	0.4795
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	-.01 (3%)
		95% confidence interval	-0.62;0.49
		p-value	0.8106
	ADAS-Cog 13	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	-0.58 (-11%)
		95% confidence interval	-1.58;0.42
		p-value	0.2536

		Comparison groups	*High dose vs Placebo*
		Difference from placebo	-0.588 (-11%)
		95% confidence interval	-1.61;0.43
		p-value	0.2578
	ADCS-ADL-MCI	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	0.7 (-18%)
		95% confidence interval	-0.19;1.64
		p-value	0.1225
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	0.7 (-18%)
		95% confidence interval	-0.25;1.61
		p-value	0.1506
	NPI-10	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	-1.0 (-83%)
		95% confidence interval	-2.06;-0.02
		p-value	0.0460
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	0.1 (8%)
		95% confidence interval	-0.98;1.10
		P-value	0.9071
Notes	On 21 March 2019, the Applicant publicly announced the termination of the Phase 3 clinical studies (221AD301 and 221AD302), based on the results of an interim futility analysis. No further doses were administered after the announcement.		

Table 28: Summary of efficacy for trial 221AD302 (EMERGE)

Title: A Phase 3 Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease		
Study identifier	Protocol number: 221AD302 EudraCT number: 2015-000967-15 ClinicalTrials.gov identifier (NCT number): NCT02484547	
Design	A multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase 3 study to assess the efficacy and safety of aducanumab in participants with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	78 weeks 8 weeks
Hypothesis	Superiority	

Treatments groups	High dose		Aducanumab 6 mg/kg after titration over 24 weeks (ApoE ε4 carrier) or 10 mg/kg after titration over 24 weeks (ApoE ε4 noncarrier). This was changed in protocol versions 4-6 into: 10mg/kg after titration over 24 weeks for all patients (regardless of ApoE ε4 status) 78 weeks, n=547randomised
	Low dose		Aducanumab 3 mg/kg after titration over 8 weeks (ApoE ε4 carrier) or 6 mg/kg after titration over 24 weeks (ApoE ε4 noncarrier). 78 weeks, n=543 randomised
	Placebo		78 weeks, n=548 randomised
Endpoints and definitions	Primary endpoint	CDR-SB	Change from baseline in CDR-SB score at Week 78
	Secondary endpoints	MMSE	Change from baseline in MMSE score at Week 78
		ADAS-Cog13	Change from baseline in ADAS-Cog13 score at Week 78
		ADCS-ADL-MCI	Change from baseline in ADCS-ADL-MCI score at Week 78
	Tertiary endpoint	NPI-10	Change from baseline in NPI-10 score at Week 78
Database lock	13 November 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (placebo-controlled period excluding data after 20Mar2019) Week 78			
Descriptive statistics and estimate variability	Treatment group	Placebo	Low dose	High dose
	Number of subject	547	543	548
	CDR-SB (adjusted mean)	1.74	1.47	1.35
	95% confidence interval	(1.513, 1.963)	(1.247, 1.701)	(1.124, 1.573)
	MMSE (adjusted mean)	-3.3	-3.3	-2.7
	95% confidence interval	(-3.68, -2.83)	(-3.77, -2.92)	(-3.11, -2.27)
	ADAS-Cog13 (adjusted mean)	5.162	4.461	3.763
	95% confidence interval	(4.3680, 5.9566)	(3.6620, 5.2604)	(2.9708, 4.5546)

	ADCS-ADL-MCI (adjusted mean) 95% confidence interval	-4.3 (-5.02, -3.53)	-3.5 (-4.29, -2.79)	-2.5 (-3.27, -1.79)
	NPI-10 (adjusted mean) 95% confidence interval	1.5 (0.63, 2.33)	1.0 (0.13, 1.84)	0.2 (-0.68, 1.01)

Effect estimate per comparison	Primary endpoint: Change from baseline in CDR-SB at Week 78	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	-0.26 (-15%)
		95% confidence interval	-0.57;0.04
		P-value	0.0901*
		Comparison groups	*High dose vs Placebo*
		Difference from placebo (%)	-0.39 (-22%)
		95% confidence interval	-0.69;-0.09
		p-value	0.0120
	Secondary endpoints: MMSE	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	-0.1 (3%)
		95% confidence interval	-0.65;0.48
		p-value	0.7578**
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	0.6 (-18%)
		95% confidence interval	0.00;1.13
		p-value	0.0493*
	ADAS-Cog 13	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	-0.70 (-14%)
		95% confidence interval	-1.76;0.36
		p-value	0.1962**
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	-1.4 (-27%)
		95% confidence interval	-2.46;-0.34
		p-value	0.0097
	ADCS-ADL-MCI	Comparison groups	*Low dose vs Placebo*
		Difference from placebo (%)	0.7 (-16%)
		95% confidence interval	-0.27;1.73
		p-value	0.1515**
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	1.7 (-40%)
		95% confidence interval	0.75;2.74
		p-value	0.0006
		Comparison groups	*Low dose vs Placebo*

	NPI-10	Difference from placebo (%)	-0.5 (-33%)
		95% confidence interval	-1.62;0.64
		p-value	0.3921**
		Comparison groups	*High dose vs Placebo*
		Difference from placebo	-1.3 (-87%)
		95% confidence interval	-2.45;-0.20
		P-value	0.0215**
Notes	On 21 March 2019, the applicant publicly announced the termination of the Phase 3 clinical studies (221AD301 and 221AD302), based on the results of an interim futility analysis. No further doses were administered after the announcement. * The CDR-SB in low dose group and MMSE in high dose group were both tested at 0.05 according to the pre-specified multiple testing procedure. The type I error is controlled between 0.05 to 0.1 for the secondary endpoints. ** nominal p-values		

2.5.4.3. Analysis performed across trials (pooled analyses and meta-analysis)

Meta-analysis for the primary and secondary endpoints

A meta-analysis for the primary and secondary endpoints from the placebo-controlled period combining Studies 301 and 302, excluding data after 20 March 2019 (censored dataset) was conducted. The model is the same as the primary analysis MMRM model used in each study, except of inclusion of study and study by visit interaction. The same analysis was conducted for the tertiary efficacy endpoint NPI-10.

The results of ITT censored analyses for the primary, secondary and tertiary endpoints are presented in Table 29. The pooled CDR SB data over time (ITT censored analysis) are graphically depicted in Figure 33.

Table 29: Analysis of change from baseline in primary, secondary and tertiary endpoints by MMRM - ITT population: placebo-controlled period excluding data after 20Mar2019 (pooled 221AD301 and 221AD302)[a]

		Placebo (N = 1093)	**Low dose (N = 1090)**	**High dose (N = 1102)**
CDR-SB	Baseline	2.44	2.45	2.45
	Change from baseline at Week 78 Adjusted mean Diff (%)[b] p-value (nominal)	1.64	1.42 -0.22 (-13%) 0.0392	1.46 -0.17 (-10%) 0.1055
MMSE	Baseline	26.4	26.3	26.3
	Change from baseline at Week 78 Adjusted mean Diff (%)[b] p-value (nominal)	-3.4	-3.3 0.1 (-3%) 0.7777	-3.2 0.2 (-6%) 0.2303
ADAS-Cog13	Baseline	22.172	22.506	22.325
	Change from baseline at Week 78 Adjusted mean Diff (%)[b]	5.152	4.522 -0.63 (-12%) 0.0897	4.171 -0.982 (-19%) 0.0088

	p-value (nominal)			
ADCS-ADL-MCI	Baseline	42.8	42.6	42.7
	Change from baseline at Week 78 Adjusted mean Diff (%)[b] p-value (nominal)	-4	-3.3 0.7 (-18%) 0.0311	-2.8 1.2 (-30%) 0.0004
NPI-10	Baseline	4.5	4.5	4.5
	Change from baseline at Week 78 Adjusted mean Diff (%)[b] p-value (nominal)	1.3	0.5 -0.8 (-62%) 0.0426	0.7 -0.6 (-46% 0.1044

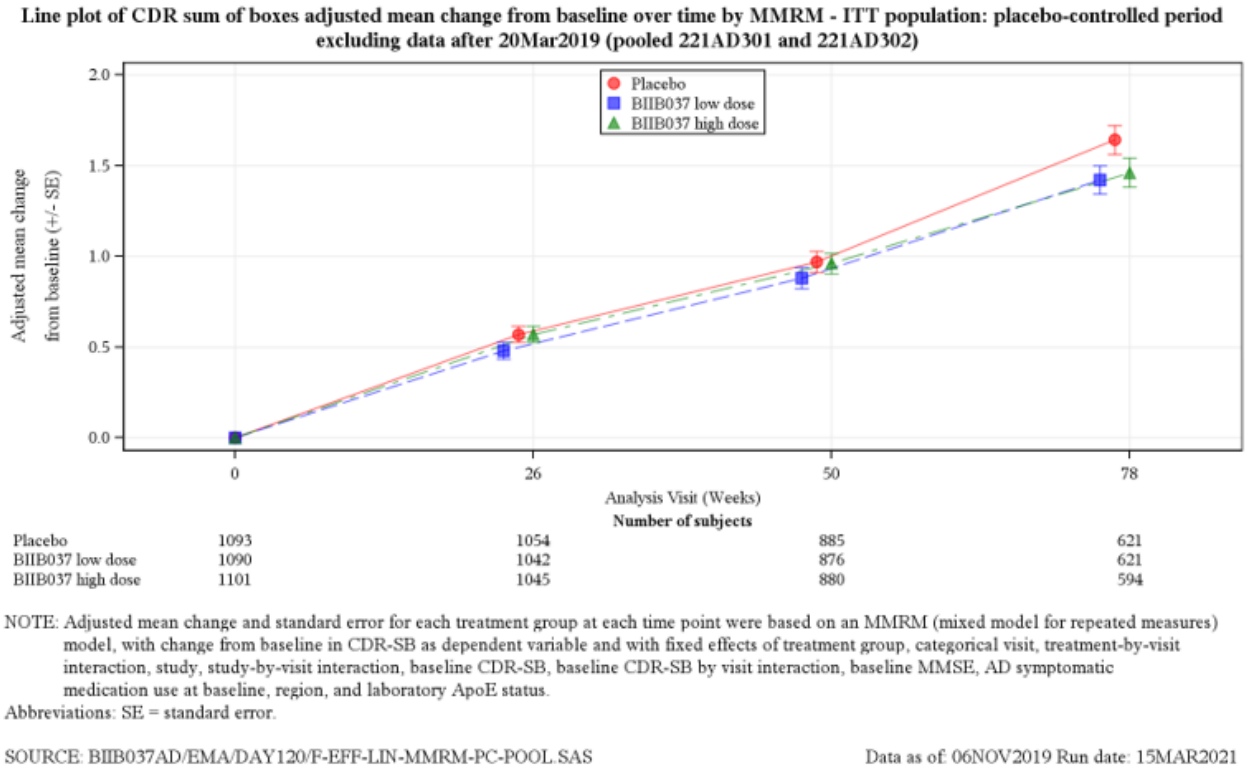
a This analysis was conducted on the pooled ITT population excluding data collected after 20 Mar 2019.

b Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm.

N: numbers of randomised and dosed participants included in the analysis.

Source: Appendix 1 Table 4, Table 5, Table 6, Table 7 and Table 8

Figure 33: Line plot of CDR sum of boxes adjusted mean change from baseline over time by MMRM - ITT population: placebo-controlled period excluding data after 20Mar2019 (pooled 221AD301 and 221AD302)



The pooled analyses are only given to provide context, and the nominally significant result for the low dose does not represent valid evidence of efficacy. To quote from the Points to Consider of Applications with meta-analyses (CPMP/EWP/2330/99): "*A retrospective meta-analysis of only two studies originally intended to stand on their own is not expected to add any useful information. In particular, a meta-analysis cannot be used to reconcile the conflicting results of one positive and one inconclusive study*" (page 3).

Exploratory analysis by EMA: Analysis by target dose

Given that the arms as randomised do not correspond univocally to target doses (see Table 30 below), the EMA has also performed an exploratory pooled analysis based on target dose.

Table 30: Target dose by randomised treatment, ApoE carrier status and consent to PV4 or higher

Randomised treatment	ApoE carrier status	Consent to PV4 or higher	Target dose
Placebo	-	-	0 mg/kg
Low dose	Carrier	-	3 mg/kg
Low dose	Non-carrier	-	6 mg/kg
High dose	Carrier	No	6 mg/kg
High dose	Carrier	Yes	10 mg/kg
High dose	Non-carrier	-	10 mg/kg

The exploratory nature of this analysis has to be emphasized since it violates the principle of analysing patients as randomised, e.g. by mixing non-carrier subjects randomised to the low dose with carrier subjects enrolled before PV4 who were randomised to the high dose.

The MMRM model use a heterogeneous Toeplitz covariance matrix to model the within-subject-variance-covariance errors as the unstructured covariance matrix did not converge for the Pooled model. Of note, modelling a random intercept for study in the pooled analysis results in an estimated random intercept of 0 for study. See Table 31 and Figure 34 below.

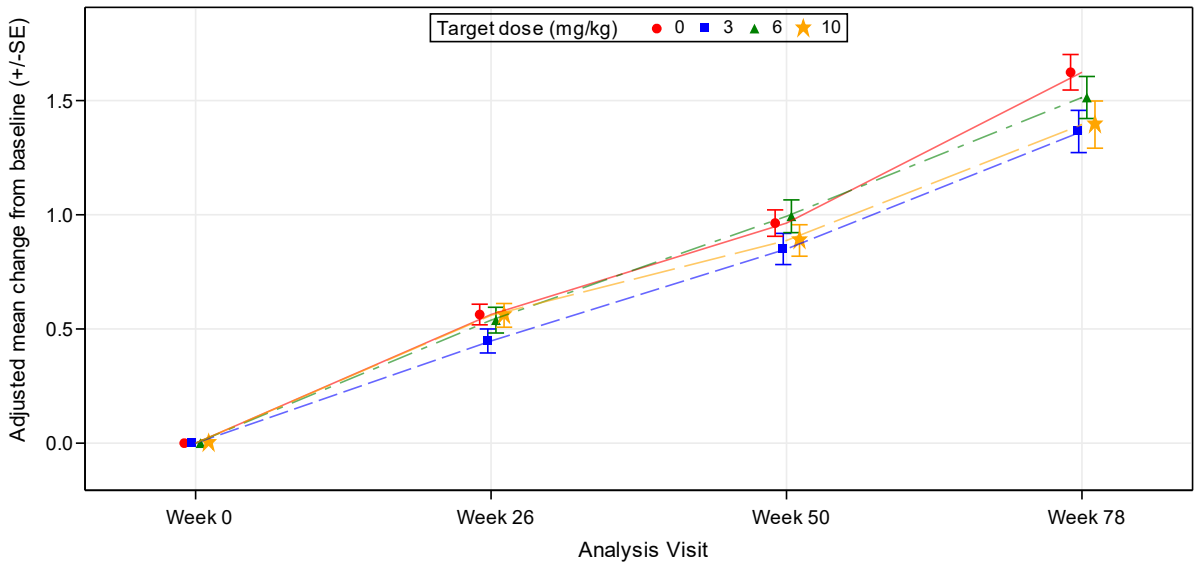
Table 31: Analysis by EMA: Change from Baseline in CDR-SB at Week 78, ITT Censored Analysis, pooled analysis based on an MMRM model with study as random effect

Pooled analysis	Placebo (0 mg/kg) (N=1093)	Target dose 3 mg/kg (N=756)	Target dose 6 mg/kg (N=687)	Target dose 10 mg/kg (N=749)
CDR-SB at baseline (mean±SD)	2.44±1.01	2.42±1.00	2.48±1.03	2.46±1.04
CDR-SB at week 78 (mean±SD)	4.07±2.33	3.77±2.30	4.06±2.43	3.71±2.37
Change on CDR-SB at week 78 (adjusted mean±SE)	1.62±0.08	1.36±0.09	1.51±0.09	1.39±0.10
Difference vs. placebo at week 78 (%)		-0.26 (-16%)	-0.11 (-7%)	-0.23 (-14%)
95% CI for difference		(-0.49; -0.03)	(-0.34; 0.12)	(-0.48; 0.02)
p-value		0.0269	0.3426	0.0700

Results were based on an MMRM (mixed model for repeated measures) model, with change from baseline in CDR-SB as dependent variable, with random intercept for study for the pooled model, and with fixed effects of target dose, categorical visit, target dose by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, and region.

The following Figure shows the estimated CDR-SB mean change from baseline over time based on the pooled MMRM analysis with a random intercept for study.

Figure 34: Analysis by EMA: Line plot of CDR-SB adjusted mean change from baseline over time



It is noted that the effect is non-significant for the proposed target dose of 10 mg/kg and that a clear evidence of dose-response is lacking.

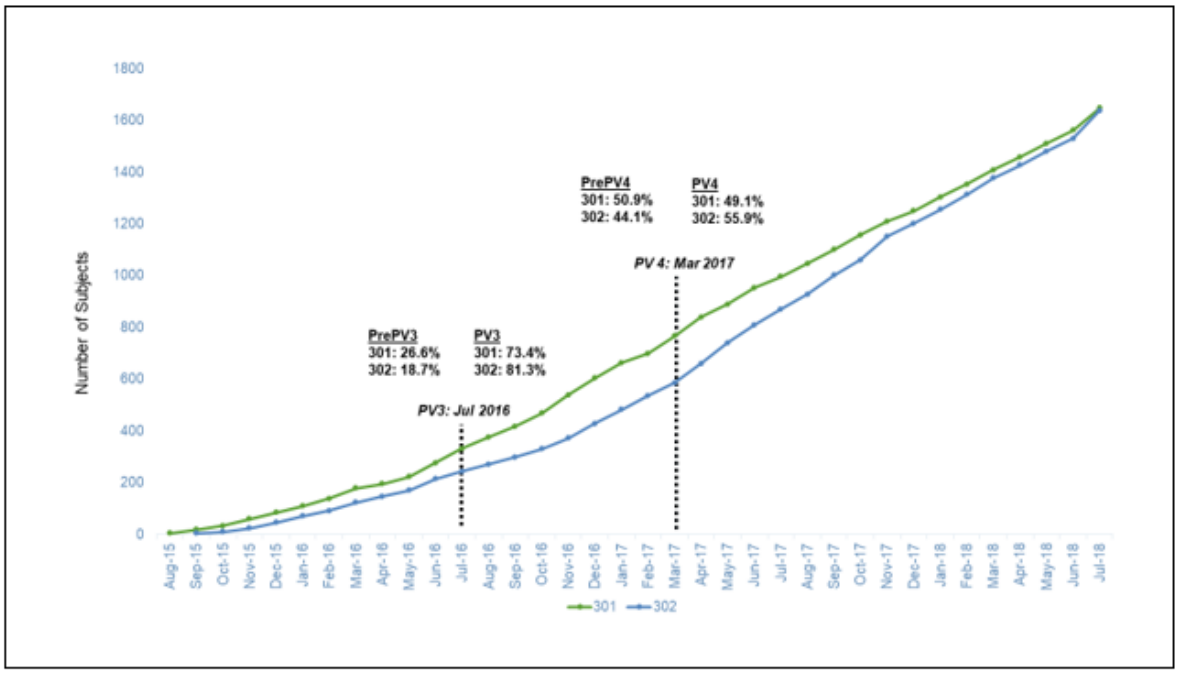
Post hoc analyses to explore the discrepancy between Study 301 and Study 302

The Applicant conducted many post-hoc analyses with the intent of exploring the Study 301 and Study 302 had discordant results. The analyses lack pre-specification and are all to be considered exploratory.

The two main factors explored for their potential to have contributed to the different results of Study 301 and 302 are an imbalance in the effect of a small number of participants with rapid progression (discussed above) and differences in dosing, discussed below.

Study 301 started 1 month earlier than Study 302, and enrolment in Study 301 continued ahead of that in Study 302 (i.e. Study 301 had more participants enrolled earlier). PV3 (changing ARIA management and allowing more patients to continue/resume dosing) and PV4 (redefining the high dose for the ApoE carriers from 6 mg to 10 mg) were finalised on the same date in both studies (26 July 2016 and 24 March 2017, respectively). However, the implementation of each protocol amendment across sites and countries took place over an extended period of approximately 6 months. Due to the differences in the timing of study initiation and enrolment, both PV3 and PV4 influenced a slightly higher percentage of participants in Study 302 (81.3% and 55.9%, respectively) than in Study 301 (73.4% and 49.1%, respectively), see Figure 35 (the green line is Study 301, the blue line is Study 302).

Figure 35: Phase 3 Enrolment and Timing of Protocol Amendments Affecting Dosing



Abbreviations: PV3 = participants that consented to protocol version 3 or higher on or prior to week 12; prePV3 = participants that did not consent to protocol version 3 or higher on or prior to week 12; PV4 = participants that consented to protocol version 4 or higher on or prior to week 16; prePV4 = participants that did not consent to protocol version 4 or higher on or prior to week 16.
Note: Protocol Version 3 was finalised on 26 July 2016, and Protocol Version 4 was finalised on 24 March 2017. Implementation across sites and countries took place over an extended period of approximately 6 months with a large range across sites/countries.
Source: Appendix G7 Table 15

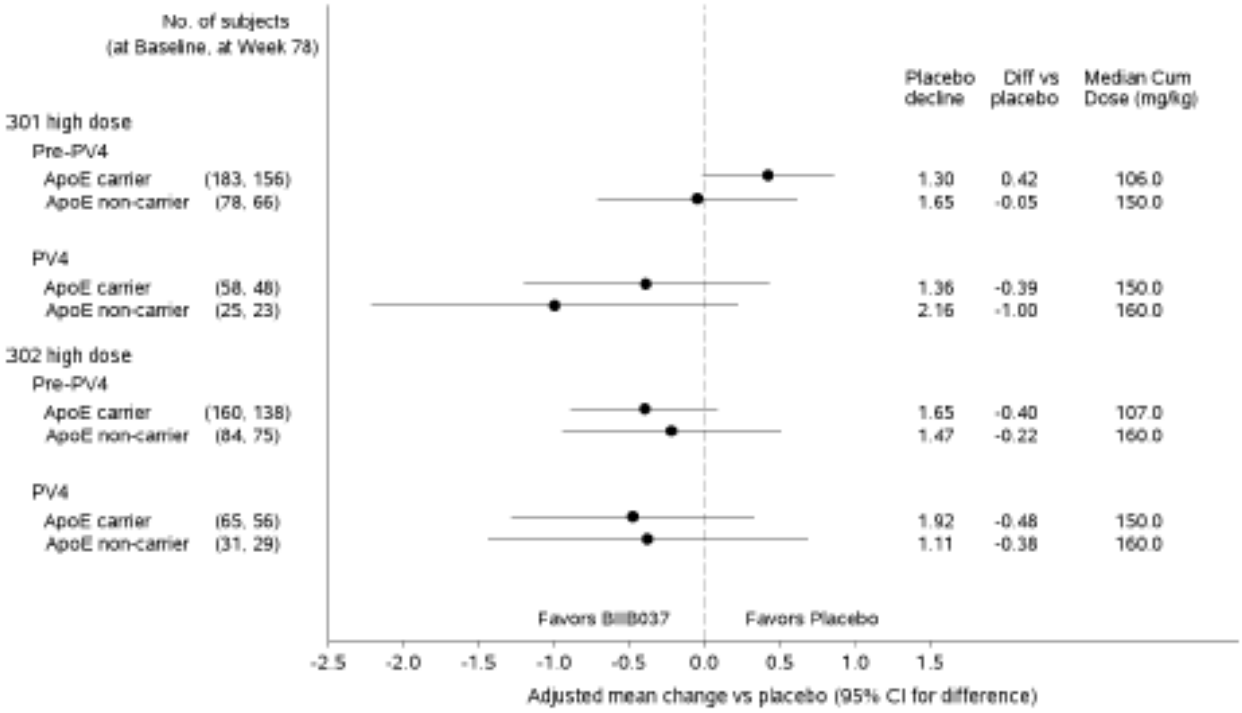
The effects of the protocol changes are reflected in the doses actually received. The mean cumulative dose received up to Week 78 was lower in the pre-PV4 high dose groups (104.4 mg/kg in Study 301; 109.5 mg/kg in Study 302) compared with the post-PV4 high dose groups (129.8 mg/kg in Study 301; 127.8 mg/kg in Study 302), see Table 32.

Table 32: Dose Information Up to Week 78 by PV4 Subset - ITT Population That Have Had Opportunity to Complete Week 78 by 20Mar2019: Placebo-Controlled Period (made by the assessor)

	Pre-Protocol Version 4		Protocol Version 4	
	Study 301	**Study 302**	**Study 301**	**Study 302**
N	262	244	83	96
Cumulative dose received up to Week 78				
Mean (SD), mg/kg	104.4±48.05	109.5±48.10	129.8±45.85	127.8±47.74
Median	114	118	153	153
Number of 10 mg/kg received up to week 78				
Mean (SD)	6.5±5.36	7.3±5.46	10.8±4.68	10.5±5.07
Median	6	8	13	13

The Applicant has also submitted efficacy results stratified for the same two variables. Interestingly, the same discordance of results observed in the overall ApoE carrier subgroups is also present when only looking at the pre-PV4 dataset (see Figure 36, with results for high dose Study 302 being similar in pre-PV4 and PV4 datasets), which is not in line with the argument of the Applicant. In particular, the dose actually received by pre-PV4 ApoE carriers assigned to the high dose is similar (as expected given stratification by protocol version) but the results are discordant (see below).

Figure 36: Results from Studies 301 and 302, high dose, by protocol version and ApoE status



The Applicant's position is that the difference in the efficacy outcome between main studies 301 and 302 could be explained by the dose actually administered. However, both the mean cumulative doses (100.4 vs 103.3 mg/kg) and mean number of 10 mg/kg doses (7.1 vs 7.5) were almost identical in high dose groups in the two studies, as shown in Table 33. The post-hoc finding of numerically higher percentage of participants spent ≥ 10 uninterrupted infusions at steady state in Study 302 compared to Study 301 (111/547 = 20% versus 81/553 = 15%) can be only considered exploratory given complete lack of pre-specification and the risk that the significance of this specific cutoff is a data-driven hypothesis.

Table 33: Summary of Cumulative Dose and Number of 10 mg/kg by Treatment by Study in the Placebo-Controlled Period (ITT Population)

	Study 301		**Study 302**	
	Low Dose (N=547)	**High Dose (N=555)**	**Low Dose (N=543)**	**High Dose (N=547)**
Cumulative dose, mg/kg				
Mean (SD)	52.9 (24.55)	100.4 (47.67)	51.8 (25.28)	103.3 (48.47)

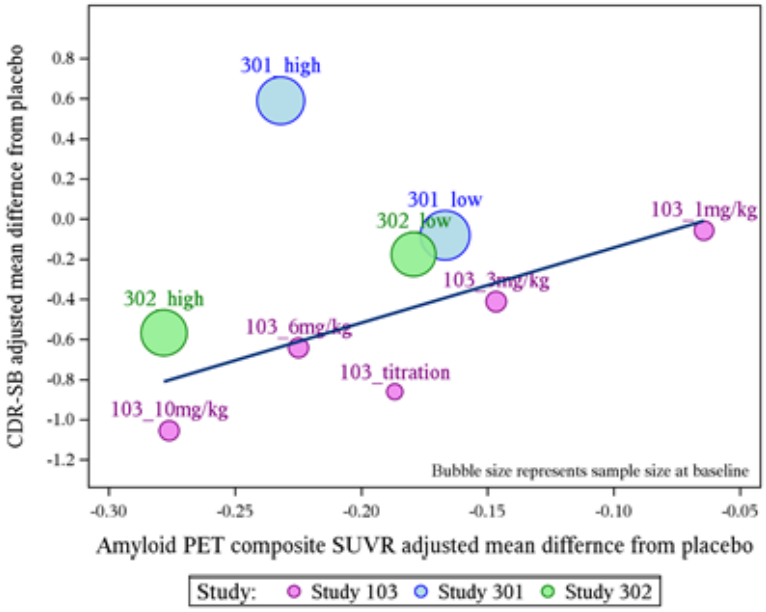
Median	56	110	53	110
Number of 10 mg/kg				
Mean (SD)	-	7.1 (5.04)	-	7.5 (5.13)
Median	-	7	-	8

Sources: Study 221AD301 Placebo-Controlled CSR Table 69 and Study 221AD302 Placebo-Controlled CSR Table 69.
CSR = clinical study report; SD = standard deviation; ITT = intention to treat.

Treatment-arm-level correlation between amyloid reduction and clinical endpoints

The Applicant presented an argument whereby the results of Study 301 should be considered an outlier, and the true effects of the high-dose Aducanumab is characterised by the results of Study 302. In support of this, the Applicant proposed that – if the correlation between amyloid reduction and clinical benefit as measured by CDR-sb is characterised – at a study arm level – by a regression line based on Study 103 and Study 302, the high dose arm of 301 would appear as an outlier (Figure 37 below).

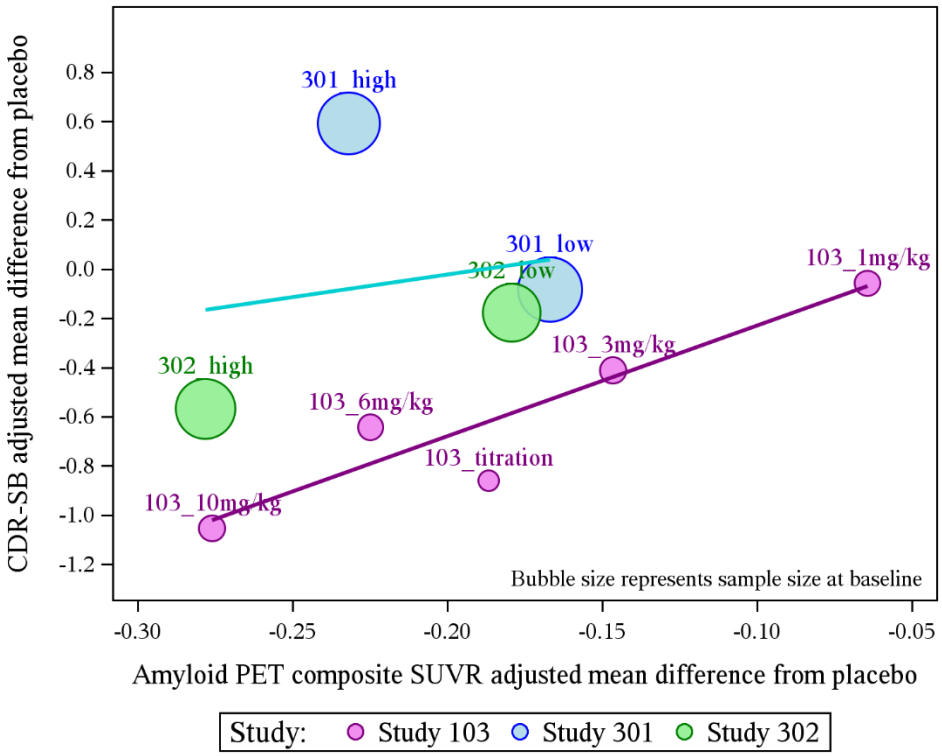
Figure 37: Study-arm level correlation between differences from placebo in amyloid PET and CDR-sb, with a regression line that excludes high dose of Study 301



NOTE 1: Due to the different study design, Week 78 was used for Studies 301 and 302, and Week 54 was used for Study 103.
NOTE 2: 18-F-florbetapir amyloid PET subpopulation was used for Studies 301 and 302. ITT population with non-missing baseline CDR-SB and PET was used for Study 103.
NOTE 3: Study 301 high dose group data point was plotted but not used for the regression line.
SOURCE: BIIB037AD/EMA/DAY120/F-CORR-GRPLV-PET-CDR-PC-NEW.SAS Data as of: 06NOV2019 Run date: 25MAR2021

This presents a circular argument: if one of the two discordant pieces of pivotal evidence is discarded, it will necessarily appear as the outlier. Furthermore, the dose-response results from Study 103 were the reason the pivotal studies were conducted, and should not be used to confirm themselves. Accordingly, upon request the Applicant replicated the plot, this time with separate regression lines from phase 1 and phase 3 (see Figure 38 and Table 34 below).

Figure 38: Study-arm level correlation between differences from placebo in amyloid PET and CDR-sb, with separate regression lines from phase 1 and phase 3



The plot displays that the correlation observed in the hypothesis-generating Study 103 is not replicated in the pivotal Studies, which show an almost flat line.

The Applicant also includes calculations of the study-arm level correlations that include results with other products (see Table 34 below). It is observed that the estimated correlations are mostly weak or moderate, and the Applicant has not demonstrated to have adopted a systematic, comprehensive search strategy, nor that the same underlying correlation must exist between different products. It should be also pointed out that independent published research reached different conclusions regarding the correlation between amyloid reduction and clinical benefit (Ackley et al, 2021).

Table 34: Group level correlation between treatment difference from placebo in amyloid PET centiloid and CDR-SB in Aducanumab, Lecanemab and Donanemab

	Weighted Spearman correlation coefficient (a)	Excluding Aducanumab 301 high dose data point
Separately on		
Aducanumab 103 study	0.94	Not applicable
Aducanumab phase 3 studies	0.39	1.00
Lecanemab 201 study	0.78	Not applicable
Pooled on		
Aducanumab	0.35	0.81
Aducanumab adjusting for study indicator (b)	0.47	0.94
Pooled on		
Aducanumab and Lecanemab	0.52	0.84
Aducanumab and Lecanemab adjusting for study indicator (c)	0.61	0.94
Pooled on		
Aducanumab, Lecanemab and Donanemab	0.55	0.73
Aducanumab, Lecanemab and Donanemab adjusting for study indicator (d)	0.64	0.93

NOTE 1: Amyloid PET difference from placebo is treatment effect on Aß PET expressed in centiloids, a standardized scale that enables comparison across studies.
NOTE 2: Due to different Aducanumab study designs, Week 54 was used for 103, Week 78 was used for phase 3 (which has a 26-week titration period before reaching target dose). Treatment effects were from MMRM models based on the amyloid PET populations.
(a) Sample size at baseline of each group was used as the weight.
(b) Partial correlation adjusting for study indicator of Aducanumab 103 or Aducanumab phase 3.
(c) Partial correlation adjusting for study indicator of Aducanumab 103, Aducanumab phase 3 or Lecanemab.
(d) Partial correlation adjusting for study indicator of Aducanumab 103, Aducanumab phase 3, Lecanemab or Donanemab.

Furthermore, as reported above for both studies, the individual-level correlation between amyloid reduction and clinical benefit is negligible, which further lowers the credibility of the argument presented.

Analyses investigating potential effects of functional unblinding due to ARIA

To evaluate the treatment effect in the ARIA and non-ARIA groups, a subgroup analysis was conducted using all placebo participants in both the ARIA and non-ARIA analysis. The same MMRM model as in the primary analysis for CDR SB was appliedin Table 35. It is difficult to conclude on the relationship between ARIA and the primary efficacy endpoint. The most favourable outcomes were seen in study 302: in the non-ARIA high dose group and ARIA Low-dose group. This indicates randomness instead of systematic bias in favour of aducanumab from functional unblinding associated with ARIA.

Table 35: Treatment difference in CDR-SB at Week 78 by ARIA status (ITT population excluding data after 20 March 2019)

	Non-ARIA		ARIA	
	Diff vs placebo[a] (%)		Diff vs placebo[a] (%)	
Study	Low dose	High dose	Low dose	High dose
Study 301	-0.14 (-9%)	0 (0%)	-0.27 (-18%)	0.10 (6%)
Study 302	-0.12 (-7%)	-0.62 (-36%)	-0.56 (-32%)	-0.09 (-5%)
Pooled	-0.13 (-8%)	-0.30 (-18%)	-0.41 (-25%)	0 (0%)

[a] Difference vs placebo at Week 78. Negative percentage means less progression in the treated arm.

2.5.4.4. Clinical studies in special populations

Most relevant special populations are patients in older age (age 65-74 and ≥75 years). No effect of age was seen. The effects of renal or hepatic impairment on aducanumab's clearance were not studied, since aducanumab is not expected to undergo renal elimination or metabolism by hepatic enzymes. Because of this, no dose adjustments are foreseen in these groups of patients. Aducanumab was not studied in paediatric patients, as agreed to by both FDA and EMA in their respective paediatric study waivers.

2.5.5. Discussion on clinical efficacy

Design and conduct of clinical studies

The main studies of the clinical development program where study 103, 301 and 302.

Study 103 was a phase 1b, randomized, double-blind, placebo-controlled multiple-dose study to assess the safety, tolerability, PK and PD of aducanumab in patients with MCI due to AD or mild AD. The study had a LTE.

Studies 301 and 302 were two identically phase III studies. Both had a randomised, multicentre placebo-controlled parallel-group study design of 78-weeks placebo-controlled period. Subjects could enter a LTE wherein subjects on placebo were randomised to switch a low or high dose aducanumab. During the LTE, the study remained blinded. The patients included in Studies 301 and 302 were patients with MCI due to AD or mild AD with a confirmed amyloid load. A subset of patients was also included in a PET-sub study wherein a serial assessment of brain Aβ plaque levels by Aβ PET was conducted.

In a previous scientific advice, there were some reservations whether the duration of the main studies of 18 months would be sufficient to detect a robust treatment effect. In particular, when mostly MCI due to AD patients are recruited, a slower progression rate is expected, and the study duration might not be long enough to demonstrate a treatment difference.

The Applicant presented Study 302 as the study on which claims of efficacy are based. However, both studies were identical; thus formally, they have the same weight for the assessment of the of evidence for efficacy.

Study participants <-> Target population

The in- and exclusion criteria adequately reflect the target population of patients with MCI due to AD or mild AD. Only patients with confirmed amyloid pathology were included. About 80% of the patients included had a diagnosis of MCI due to AD.

The Applicant changed the initially claimed indication into (changes in bold): *"Aduhelm is indicated as a disease-modifying treatment in adult patients with Alzheimer's disease at the mild cognitive impairment (MCI) or mild dementia stage*. ***Presence of amyloid beta pathology should be confirmed as part of diagnosis.***" The proposed indication reflects the population of patients that was included in the Phase III Studies.

The study population was enriched, i.e. the presence of amyloid load measured by the PET scan was a mandatory inclusion criterion. Aducanumab is targeting amyloid beta and thus, amyloid should be present in patients intended to be treated. The presence of amyloid is included in the indication.

Outcomes

The primary endpoint is the CDR-SB; this is an accepted primary endpoint for AD. Secondary endpoints are the MMSE, ADAS-Cog 13 and the ADCS-ADL-MCI. Together, these scales are frequently used in AD

studies and cover the cognitive, functional, behavioural and psychiatric domains of AD and allow a conclusion on the clinical relevance of aducanumab in the treatment of AD.

Cerebral Aβ Plaque Level, as measured by PET scanning, is a tertiary endpoint. SUVR is an established quantitative measure of Aβ PET images. In the case of Aβ PET imaging, the SUVR score serves as an indicator for cerebral amyloid load.

Sample size

Assumptions for the sample size calculation were derived from an interim analysis of study 103. Based on the assumptions, the calculation is correct. A difference of a 0.5 point in CDR-SB was the effect size considered worthwhile to detect, i.e. is considered being clinically relevant. A sample size of 450 per treatment group was planned. The sample size was reassessed during an interim analysis with about 10% of data, resulting in a sample size increase due to the observation of higher variance.

Randomisation and blinding

Randomisation and blinding procedures are considered adequate.

Statistical methods

The definitions of the initial analysis populations are considered standard and adequate. Due to early termination of the studies, modifications were defined: an ITT censored, Opportunity-to-Complete (double-blind) and an ITT uncensored population. The ITT censored population is considered the pivotal population as the data collected after 20 March 2019 are excluded. The data collected in this population was still double-blinded and similar to the futility analysis. The Opportunity-to-Complete and uncensored population are considered sensitivity analysis.

The primary endpoint was analysed using an MMRM model. Given the amount and reasons for missing data and how this is handled, this is an acceptable approach. Addition of randomisation factors and baseline value in the model is standard. Inclusion of baseline MMSE and concomitant AD medication as covariates is acceptable as these are indicators of disease severity which may be effect modifiers. The covariance matrix used is agreed. The MMRM model assumed that data was missing at random, is acceptable. In addition, the sensitivity analysis testing is acceptable.

Secondary endpoints were analysed by the same primary analysis model and sensitivity and subgroup analysis.

Multiplicity, due to two-dose arms and primary and secondary endpoints is handled by a hierarchical closed testing sequence. After a successful test of the primary endpoint for the high dose, both the primary endpoint for the low dose and the first secondary endpoint for the high dose could be tested at full alpha. This does not control the study-wise type I error rate. Since in the description of the method, the doses are mentioned before the secondary endpoints, for the assessment of study 302, the sequential testing at an appropriate level of type I error control stops at the negative primary analysis of the low dose and all secondary endpoints are tested nominally only.

Conduct of the study

Data on screening failures were provided upon request. In total, there were 9634 screening failures for both pivotal studies. The majority of screening failures (n=6223, 64.7%) for both studies was because patients did not meet the clinical criteria for MCI due to AD or mild AD according to NIA-AA criteria or did not meet the requirements of the cognitive screenings outcomes. About 15% (n=1502) of screening failures were patients with a negative PET scan. In 3.1% (n= 301) of cases, the reason for exclusion was brain MRI findings at screening. For approximately 25% of patients in both studies, the major protocol violation concerned the informed consent. Several informed consent forms for sub studies had to be provided, also if a patient was not participating in a substudy. In addition, after updates/protocol

revisions, the informed consents needed to be re-consented, but the study partner was not always present. Both were major protocol violations. However, none of the patients was randomised into a study without providing the main informed consent form.

In both studies, 13-14% of patients stopped with concomitant symptomatic AD medication before they entered the studies. Patients stopped concomitant AD medication at least 8 weeks before the CDR-SB baseline assessment. It is assumed that this is also the case for the other baseline clinical assessments. Three patients seemed not to have discontinued their symptomatic AD medication. However, the impact of these three patients on the totality of baseline data may be considered negligible.

When the Phase III studies were running for over 2.5 years, amendments in the dosing were made. At that time, about half of the patients were included. Initially, the aducanumab dose depended on ApoE ε4 status, the most important genetic risk factor for AD. However, the dose for ApoE ε4 carriers was adjusted based on the results of an additional cohort in Study 103 (titration of the 10mg/kg dose), i.e. in this study the incidence of ARIA-E was reduced compared to the 10 mg/kg dose if it was started at once. Herewith, the dose in ApoE ε4 carriers on 6 mg/kg was up titrated to 10 mg/kg.

There was a considerable potential risk of functional unblinding (patients and care-givers') due to ARIA management. The patients/caregivers were informed that ARIA would not occur with placebo before the study. During the course of the studies, ARIA occurred up to 40% in the high dose group and 10% in placebo. To monitor and ensure safety, patients with ARIA may have dosing suspended as well as additional follow-up MRIs. Investigators, caregivers and patients likely assumed that patients with the ARIA follow up interventions were on active treatment. Investigators responsible of efficacy ratings were blinded to ARIA management; the caregivers and patients were not. Expectation effects may have impacted patient motivation in the testing situation and answers from caregivers in the interview situation. It is, however, difficult to conclude on the relationship between ARIA and the primary efficacy endpoint. The most favourable outcomes were seen in study 302: in the non-ARIA high dose group and ARIA Low-dose group. This indicates randomness instead of systematic bias in favour of aducanumab from functional unblinding associated with ARIA.

Efficacy data and additional analyses

Futility analysis

A pre-defined futility analysis was conducted (26 December 2018) when 945 (57%) patients from Study 301 and 803 (49%) of patients from Study 302 completed the Week 78 visit. As the futility criteria were met, the DSMB recommended stopping the studies 103, 301 and 302. This was implemented at 21 March 2019. The April Transfer ITT censored analysis is the ITT population, excluding the data collected after 20 March 2019. This population is discussed in this assessment report since the data collection in this group was still conducted double-blinded and similar to before the futility analysis.

Completion

53-57% of the patients completed the studies. For the majority of patients, the reason for not completing the study was the early study termination. The second most reason in both studies for not completing the study was 'adverse event', which was dose-dependent.

Treatment effects

Study 103

The efficacy results should be interpreted with caution since they were exploratory, and the number of patients was limited. Nevertheless, the results established the proof of concept. Also, a dose-response relationship was observed. The most optimal dose is the fixed 10 mg/kg dose. However, the highest

doses do not seem to reach a plateau; thus, it cannot be excluded that higher doses would be more efficacious. The results of this study justified proceeding into the phase III studies, although the conclusion that the study demonstrates that the proposed dose of 10 mg/kg is the optimal dose, is questioned. In Study 103, a dose-related effect was observed on the amyloid load. However, a plateau was not reached, suggesting that higher doses than 10 mg/kg could be more effective. It cannot be excluded, under the assumption that aducanumab is truly effective, that the 10 mg/kg dose is at the lower side of the dose-effect curve.

Study 301

There was no difference in change from baseline at Week 78 in CDR-SB between aducanumab low-dose and placebo; -0.18 (-12%, p=0.2250). Also, there was no difference in change from baseline between high-dose and placebo was 0.03 (2%, p=0.8330). Likewise, on the cognitive and functional subdomains of the CDR, no differences between aducanumab (low/high dose) and placebo were found.

Since the primary endpoint results were not statistically significant, the secondary endpoint results cannot be claimed to be significant, given the closed test procedure. Results of secondary endpoints resented are considered being purely descriptive. No difference between placebo and the two treatment arms of aducanumab were observed after 78 weeks in any of these secondary endpoints i,e, MMSE, ADAS-Cog 13 and ADCS-ADL-MCI or tertiary endpoint; NPI-10.

The adjusted mean changes from baseline in Aβ PET composite SUVR at Week 78 relative to placebo were -0.167 [p<0.0001] for the low dose and -0.232 [p<0.0001] for the high dose. The reduction in cerebral amyloid load did not show an association with the primary endpoint. On the one hand, this was not expected given that the clinical endpoints were not met; on the other hand, the result of study 103 at least suggested such a relationship, which could not be confirmed.

Slightly less than half of the patients from the placebo-controlled phase rolled over into LTE. Furthermore, the long term extension (LTE) was terminated after 56 weeks, limiting the interpretation of the long term treatment effect of aducanumab.

Study 302

The difference in change from baseline at Week 78 in CDR-SB between aducanumab low-dose and placebo was -0.26 (-15%, p=0.0901). The difference in change from baseline between high-dose and placebo was -0.39 (-22%, p=0.0120).

Note that due to the closed test procedure, as the difference for the lower dose group was not statistically significant, the results of the secondary endpoints presented are descriptive and their inferential interpretation is not agreed. At Week 78, the difference between aducanumab high-dose group and placebo based on change from baseline on the MMSE was 0.6 (-18%, p=0.0493), on the ADAS-Cog13 -1.400 (-27%, p=0.0097) and in ADCS-ADL-MCI 1.7 (-40%, p=0.0006). This was -1.3 (-87%, p=0.0215) for the NPI-10.

The adjusted mean change from baseline in Aβ PET composite SUVR at Week 78 relative to placebo was for the low dose; -0.179 [p<0.0001] and for the high dose; -0.278 [p<0.0001]. A negligible association between change in cerebral amyloid-beta load and change in the primary endpoint was found. This is unexpected since the primary endpoint in Study 302 was met for the high dose and the results of study 103 were also pointing at such a relationship. Considering the weak to null individual-level correlation between change in amyloid load and clinical outcomes in both studies, the relevance of the proposed mechanism of action is questioned.

The change in CDR-SB was statistically significantly less for the high dose as compared to placebo (p=0.012). However, the difference of -0.39 points (relative difference of 22%) is small, of questionable clinical relevance, and the difference of 0.5 points on the CDR-SB – used at the planning stage - was not

achieved. The 0.5 point difference on the CDR-SB as a minimally clinical relevant difference is also recommended in the literature (Andrews et al, 2019)[1]. Based on an interim analysis of Study 103, the annual progression was expected to be around 0.6 points on the CDR-SB. Although the secondary endpoints are only numerically supportive, the issue of clinical relevance applies as well. In addition, it is not shown that aducanumab treatment results in stabilisation of cognitive decline since patients do show progression over time.

As for Study 301, the long term extension (LTE) was terminated after 56 weeks and is too limited in both duration and sample size to allow a meaningful characterisation of the long term treatment effect of aducanumab.

Sensitivity analyses

The results of the sensitivity analyses are consistent with the results of the primary analysis.

Concomitant medications

A fairly substantial amount of patients included used concomitant AD medication during the clinical trial. From the subgroup analyses, a complementary effect of concomitant AD medication on aducanumab seems not present.

Sleep disturbances were shown to impact the progression of AD. Several analyses indicated that no conclusions on the possible influence of changes in sleep-promoting agents can be made. This was also due to low numbers in subgroups of patients changing medication. From this subgroup analysis a confounding effect of concomitant sleep-promoting medication seems not present.

Post-hoc analyses

Numerous post-hoc analyses were performed, reviewing the individual study results for consistency/difference. Although the definitions of the study populations are acceptable and most post-hoc analyses follow the primary analysis model, they are considered being only exploratory. Since the futility analysis was based on pooled data, a meta-analysis of pooled data using study as factor was requested. The pooled analysis failed to confirm the observed effect in study 302 for the high dose, it did show a numerical effect on CDR-SB but was not statistically significant. It does meet this threshold for the low dose. Since it is preceded by a futility stop at interim, based on post-hoc pooled analysis, and it involves one positive and one negative study, it is at best supportive/explorative rather than confirmatory (see also the Reflection paper on application with meta-analysis). Furthermore, there does not appear to be a dose-effect relationship for CDR-SB in the pooled analysis, lowering the credibility of this finding even further.

Main arguments posed by the Applicant for conflicting findings in Studies 301 and 302

The Applicant assumes that two factors have contributed to the different results of Study 301 and 302: 1) an imbalance in the effect of a small number of participants with rapid progression and 2) differences in dosing.

1) Rapid progressors were defined as patients with a decline of >8 points on the primary endpoint at Week 78. There were 18 rapid progressors in Study 301; 4 on placebo, 5 on the low dose and 9 on the high dose. There were 13 rapid progressors in Study 302; 4 on placebo, 4 on the low dose and 5 on the high dose. There is no consensus definition of "rapid progressors". However, several definitions give similar results. More importantly, excluding patients based on observed post-randomisation events is

[1] Scott Andrews et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials (2019). Alzheimer's & Dementia: Translational Research & Clinical Interventions 5; 354-363.

not acceptable and it is very well known to have the potential to bias the analysis. Furthermore, the effect of removing these few patients is small.

2) The reasoning that -because of the adjusted aducanumab high dose for APoE ε4 carriers- fewer patients could reach the target dose of 10 mg/kg is not supported. Both the mean cumulative doses (100.4 vs 103.3 mg/kg) and mean number of 10 mg/kg doses (7.1 vs 7.5) were almost identical in high dose groups in both studies. The Applicant's approach to create additional subgroups groups taking into account dose interruptions, dosing modifications and clinical progression variables lacks clear mechanistically plausible rationale, and again ends up selecting patients based on post-randomisation events, which is at risk of bias and does not allow causal interpretations. In the analysis conducted by EMA, no robust or consistent effect, or dose-response relationship are observed. The effect observed for the highest target dose of 10 mg/kg in study 302 is not confirmed in study 301 nor in the pooled analyses and the overall results are conflicting.

Note the reasoning by the Applicant is in one direction only, i.e. the reason why Study 302 was not negative is not explored. The point is that the two studies are identical, the studies were performed in the same time period (Aug/Sep 2015-Aug 2019), and the study population did not differ. Study 301 clearly failed to show an effect, whereas in Study 302 the primary endpoint was met in the sense of that results were statistically significant but small in size.

There are no data to exclude the alternative explanation for the apparently conflicting results of the two studies: that Study 301 reflects the true effect and Study 302 is a false positive. Inherent to the randomization procedure, studies may be positive or negative when the true effect is not different from placebo

In any case, the observed effect size in Study 302 is small and not considered clinically relevant, as also concluded by the SAG.

2.5.6. Conclusions on the clinical efficacy

The totality of data does not show that aducanumab is efficacious in the treatment of MCI due to AD and Mild AD. The clinical program was prematurely terminated by the Applicant for futility. In the final analysis, based on available data up to futility announcement, two identically designed Phase III studies showed conflicting results; Study 301 did not meet its endpoint, in contrast to Study 302. The results of Study 302 are not compelling in terms of clinical relevance. Furthermore, the disease-modifying claim is not substantiated. A biomarker such as Aβ PET composite SUVR cannot be considered as a surrogate endpoint of efficacy and clinical benefit for regulatory approval. There is currently not enough evidence that the overall clinical course of the disease is modified by aducanumab.

2.5.7. Clinical safety

2.5.7.1. Patient exposure

The aducanumab clinical development programme includes seven clinical studies in AD and one clinical study in healthy volunteers. Throughout the aducanumab clinical development program for AD, 3078 subjects have received at least one dose of aducanumab.

Safety data presented includes 1806 patients exposed to aducanumab for at least one year and 129 patients exposed to aducanumab for over 3 years.

The main body of evidence for the safety of aducanumab originates from the two Phase 3 placebo-controlled clinical studies 221AD301 and 221AD302. The other four studies providing safety data in patients with AD include a single-dose first-in-human study conducted in participants with mild to moderate AD (221AD101), a single- and multiple-dose safety and PK study in Japanese participants with mild to moderate AD (221AD104), and two multiple-dose safety studies, one in participants with prodromal or mild AD (221AD103) and one in participants with MCI due to AD or mild AD (221AD205).

The applicant has pooled the safety data from the two pivotal studies, defining two datasets:

1. Pool A1 – the placebo-controlled data

- Includes all randomised participants who received at least 1 dose of study treatment (placebo or aducanumab) in the placebo-controlled period of the Phase 3 studies.

2. Pool A2 – aducanumab-treated data including both placebo-controlled and long-term OL data

- Includes all randomised participants who received at least 1 dose of aducanumab at any time in the Phase 3 studies, including placebo-controlled and/or LTE periods.

In addition, supportive analyses have been performed using Pool B, which includes all randomised participants who received at least 1 dose of aducanumab in Studies 301, 302, 103, or 104, including the placebo-controlled and long-term extension periods. The description of the safety pools is presented in Table 36.

Table 36: Description of Pool A1, Pool A2 and Pool B

Pool (total N)	Studies (planned duration) (actual duration [median])	Treatment group for safety and dose regimen in the studies (N)	Pooled treatment category (N)
Pool A1 (N=3285)	301/302 (18 months) (1.5 years)	Placebo group N=1087 Low dose group Titration to 3 mg/kg, carriers N=760 Titration to 6 mg/kg, noncarriers N=333 High dose group Titration to 6 or 10 mg/kg, carriers N=749 Titration to 10 mg/kg, noncarriers N=356	Placebo N=1087 3 mg/kg N=760 6 mg/kg N=405 10 mg/kg N=1033 Total combined aducanumab N=2198
Pool A2 (N=2757)	301/302 (up to 6.5 years) (1.3 years)	Early start low dose Titration to 3 mg/kg, carriers N=758 Titration to 6 mg/kg, noncarriers N=332 Early start high dose Titration to 6 or 10 mg/kg, carriers N=746 Titration to 10 mg/kg, noncarriers N=356 Late start low dose Titration to 3 mg/kg, carriers N=195 Titration to 6 mg/kg, noncarriers N=86 Late start high dose Titration to 6 or 10 mg/kg, carriers N=203 Titration to 10 mg/kg, noncarriers N=81	3 mg/kg N=953 6 mg/kg N=457 10 mg/kg N=1347 Total combined aducanumab N=2757
Pool B (N=2959)	301/302: up to 6.5 years 103: up to 9 years 104: 5 to 9 months (1.4 years)	See description of individual studies	<10 mg/kg N=1545 10 mg/kg N=1414 Total combined aducanumab (2959)

The focus of safety assessment in this assessment report lies on Pool A1, i.e. the placebo-controlled data.

To assess the impact of the dose, safety data for Pools A1 and A2 are presented by treatment group based on the target dose in the titration regimen, using the following categories:

- Placebo (Pool A1 only)
- Aducanumab 3 mg/kg

- Aducanumab 6 mg/kg
- Aducanumab 10 mg/kg

In Pool A1, 10% of patients did not receive their assigned target dose of 10 mg/kg, and 14.9% of patients did not receive their assigned target dose of 6 mg/kg. The applicant has also examined the incidence of adverse events per maximum dose actually received, which is presented as well.

In Pool A1, The median age was 71 across the treatment arms and the age distribution similar. Most patients were white (77.2% in the placebo group and 76.6% in the aducanumab total group). A similar percentage of patients were enrolled in the United States and Europe/Canada/Australia.

The majority of patients had MCI due to AD, in the aducanumab 6 mg/kg there were slightly more patients with mild AD compared to the other treatment groups (27.9% vs 18.1% in the aducanumab 10 mg/kg group). The imbalance seen in the ApoE e4 carrier status between the groups; i.e. in the 3 mg/kg group almost all are carriers whereas in the aducanumab 6 mg/kg group almost all non-carriers, is explained by the planned assignment of ApoE ε4 carrier and noncarriers to different dosing schedules (in at least some of the randomisations). Approximately 50% of patients in all treatment arms were taking symptomatic AD medication at baseline. The median time since AD diagnosis was less than a year and balanced between the treatment groups.

The most common medical history preferred terms were expected for the age of a population of participants with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia and included hypertension (placebo: 42.2%; aducanumab: 43.1%), depression (placebo: 24.7%; aducanumab: 25.7%), hyperlipidaemia (placebo: 18.8%; aducanumab: 19.2%), hypercholesterolaemia (placebo: 19.7%; aducanumab: 19.0%), and osteoarthritis (placebo: 17.2%; aducanumab: 18.6%). Despite the fact that approximately 42% of patients participating in clinical trials had hypertension at baseline no medications used to treat hypertension were reported among the most commonly used treatments.

2.5.7.2. Adverse events

An overview of the treatment-emergent adverse events by frequency is summarized in Table 37. The data are presented for Pool A1 and Pool A2.

Table 37: Overall summary of adverse events – Pool A1 and Pool A2

	Placebo N = 1087	Aducanumab 3 mg/kg (N=760)	Aducanumab 6 mg/kg (N=405)	Aducanumab 10 mg/kg (N=1033)	Aducanumab total (N=2198)
Pool A1					
Number of subjects with any event	945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7)
Severity[a]					
Mild	445 (40.9)	252 (33.2)	122 (30.1)	331 (32.0)	705 (32.1)
Moderate	408 (37.5)	328 (43.2)	177 (43.7)	465 (45.0)	970 (44.1)
Severe	92 (8.5)	120 (15.8)	48 (11.9)	150 (14.5)	318 (14.5)
Related event[b]	273 (25.1)	373 (49.1)	148 (36.5)	530 (51.3)	1051 (47.8)
Serious event	151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
Related serious event	8 (0.7)	9 (1.2)	7 (1.7)	21 (2.0)	37 (1.7)
Events leading to drug discontinuation	45 (4.1)	65 (8.6)	45 (11.1)	91 (8.8)	201 (9.1)
Events leading to study withdrawal	31 (2.9)	32 (4.2)	27 (6.7)	38 (3.7)	97 (4.4)
Deaths, n (%)	5 (0.5)	3 (0.4)	0	8 (0.8)	11 (0.5)
Pool A2		N= 953	N=457	N=1347	N=2757
Number of subjects with any event		855 (89.7)	389 (85.1)	1194 (88.6)	2438 (88.4)
Severity[a]					
Mild		276 (29.0)	131 (28.7)	385 (28.6)	792 (28.7)
Moderate		412 (43.2)	187 (40.9)	592 (43.9)	1191 (43.2)
Severe		166 (17.4)	71 (15.5)	217 (16.1)	454 (16.5)
Related event[b]		467 (49.0)	161 (35.2)	663 (49.2)	1291 (46.8)
Serious event		158 (16.6)	80 (17.5)	210 (15.6)	448 (16.2)
Related serious event		16 (1.7)	8 (1.8)	28 (2.1)	52 (1.9)
Events leading to drug discontinuation		82 (8.6)	49 (10.7)	124 (9.2)	255 (9.2)
Events leading to study withdrawal		43 (4.5)	34 (7.4)	49 (3.6)	126 (4.6)
Deaths, n (%)		4 (0.4)	4 (0.9)	11 (0.8)	19 (0.7)

NOTE: A subject can appear in more than one category.
(a) Each subject was counted once at maximum severity.
(b) Related to study drug as assessed by the investigator.

The incidence of adverse events by maximum dose actually received was similar to the incidence per target dose: 91.3% in the aducanumab 3 mg/kg group, 87.3% in the aducanumab 6 mg/kg group and 91.5% in the aducanumab 10 mg/kg group.

The incidences of AEs in Pool A1 by SOC are listed in Table 38, and the most commonly reported AEs by preferred term are presented in Table 39.

Note that ARIA was required to be reported as an adverse event and therefore appears in the adverse event listing, even though it might have been asymptomatic. ARIAs were to be reported under 4 terms: ARIA-E, ARIA-H microhaemorrhage, ARIA-H superficial siderosis and ARIA-H macrohaemorrhage.

Table 38: Incidence of adverse event in Pool A1 by SOC

System Organ Class	Placebo N = 1087	Aducanumab 3 mg/kg (N=760)	Aducanumab 6 mg/kg (N=405)	Aducanumab 10 mg/kg (N=1033)	Aducanumab total (N=2198)
Subjects with any event	945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7)
Nervous system disorders	460 (42.3)	444 (58.4)	193 (47.7)	648 (62.7)	1285 (58.5)
Infections and infestations	471 (43.3)	306 (40.3)	151 (37.3)	438 (42.4)	895 (40.7)
Gastrointestinal disorders	309 (28.4)	211 (27.8)	88 (21.7)	287 (27.8)	586 (26.7)
Musculoskeletal and connective tissue disorders	300 (27.6)	194 (25.5)	90 (22.2)	294 (28.5)	578 (26.3)
Injury, poisoning and procedural complications	268 (24.7)	197 (25.9)	100 (24.7)	280 (27.1)	577 (26.3)
Psychiatric disorders	265 (24.4)	200 (26.3)	89 (22.0)	255 (24.7)	544 (24.7)
General disorders and administration site conditions	201 (18.5)	124 (16.3)	59 (14.6)	192 (18.6)	375 (17.1)
Skin and subcutaneous tissue disorders	169 (15.5)	119 (15.7)	65 (16.0)	151 (14.6)	335 (15.2)
Respiratory, thoracic and mediastinal disorders	161 (14.8)	101 (13.3)	51 (12.6)	170 (16.5)	322 (14.6)
Vascular disorders	119 (10.9)	84 (11.1)	40 (9.9)	115 (11.1)	239 (10.9)
Eye disorders	111 (10.2)	81 (10.7)	43 (10.6)	105 (10.2)	229 (10.4)
Investigations	119 (10.9)	72 (9.5)	45 (11.1)	95 (9.2)	212 (9.6)
Metabolism and nutrition disorders	101 (9.3)	73 (9.6)	20 (4.9)	93 (9.0)	186 (8.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	93 (8.6)	56 (7.4)	33 (8.1)	67 (6.5)	156 (7.1)
Renal and urinary disorders	76 (7.0)	47 (6.2)	27 (6.7)	77 (7.5)	151 (6.9)
Cardiac disorders	86 (7.9)	41 (5.4)	34 (8.4)	64 (6.2)	139 (6.3)
Ear and labyrinth disorders	52 (4.8)	41 (5.4)	22 (5.4)	69 (6.7)	132 (6.0)
Blood and lymphatic system disorders	37 (3.4)	25 (3.3)	16 (4.0)	40 (3.9)	81 (3.7)
Reproductive system and breast disorders	26 (2.4)	24 (3.2)	11 (2.7)	30 (2.9)	65 (3.0)

Immune system disorders	18 (1.7)	16 (2.1)	7 (1.7)	17 (1.6)	40 (1.8)
Hepatobiliary disorders	22 (2.0)	8 (1.1)	4 (1.0)	16 (1.5)	28 (1.3)
Endocrine disorders	13 (1.2)	9 (1.2)	1 (0.2)	5 (0.5)	15 (0.7)
Product issues	2 (0.2)	8 (1.1)	1 (0.2)	2 (0.2)	11 (0.5)
Congenital, familial and genetic disorders	1 (<0.1)	2 (0.3)	1 (0.2	2 (0.2)	5 (0.2)
Social circumstances	1 (<0.1)	0	1 (0.2)	0	1 (<0.1)

NOTE 1: A subject was counted only once within each system organ class (MedDRA version 22.0).
NOTE 2: Preferred term is presented in decreasing frequency of the table's rightmost column.

Table 39: Most commonly reported AEs by PT – Pool A1

Preferred term	Placebo N = 1087	Aducanumab 3 mg/kg (N=760)	Aducanumab 6 mg/kg (N=405)	Aducanumab 10 mg/kg (N=1033)	Aducanumab total (N=2198)
Subjects with any adverse event	945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7
Headache	165 (15.2)	161 (21.2)	58 (14.3)	212 (20.5)	431 (19.6)
Fall	128 (11.8)	105 (13.8)	50 (12.3)	155 (15.0)	310 (14.1)
Nasopharyngitis	155 (14.3)	91 (12.0)	52 (12.8)	150 (14.5)	293 (13.3)
Superficial siderosis of central nervous system	24 (2.2)	91 (12.0)	23 (5.7)	151 (14.6)	265 (12.1)
Dizziness	98 (9.0)	73 (9.6)	27 (6.7)	100 (9.7)	200 (9.1)
Diarrhoea	74 (6.8)	62 (8.2)	27 (6.7)	92 (8.9)	181 (8.2)
Upper respiratory tract infection	90 (8.3)	62 (8.2)	35 (8.6)	81 (7.8)	178 (8.1)
Back pain	78 (7.2)	46 (6.1)	21 (5.2)	84 (8.1)	151 (6.9)
Urinary tract infection	74 (6.8)	53 (7.0)	20 (4.9)	60 (5.8)	133 (6.1)
Nausea	69 (6.3)	47 (6.2)	18 (4.4)	65 (6.3)	130 (5.9)
Depression	64 (5.9)	47 (6.2)	26 (6.4)	54 (5.2)	127 (5.8)
Fatigue	75 (6.9)	42 (5.5)	20 (4.9)	63 (6.1)	125 (5.7)
Arthralgia	59 (5.4)	32 (4.2)	16 (4.0)	65 (6.3)	113 (5.1)
MRI abnormalities					
Amyloid related imaging abnormality-oedema/effusion	29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	71 (6.5)	141 (18.6)	50 (12.3)	197 (19.1)	388 (17.7)
Superficial siderosis of central nervous system	24 (2.2)	91 (12.0)	23 (5.7)	151 (14.6)	265 (12.1)

NOTE 1: A subject was counted only once within each preferred term (MedDRA version 22.0).
NOTE 2: Numbers in parentheses are incidence rates per 100 subject-years. Follow-up time is calculated as the number of days from first dose of treatment until the last day in placebo-controlled period, divided by 365.25.
NOTE 3: Preferred term are presented in decreasing frequency of the table's rightmost column.

In Pool A2, the most common adverse events occurred in the SOCs nervous system disorders (aducanumab total group: 58.7%), infections and infestations (aducanumab total: 41.4%) and injury, poisoning and procedural complications (aducanumab total: 28.4%).

The most commonly reported preferred terms were the same as in Pool A1 i.e. ARIA-E (aducanumab total group 29.7%), headache (aducanumab total: 19.1%) and ARIA-H microhaemorrhages (aducanumab total:18.2%).

In Pool B, the incidence of most common adverse events was consistent with Pool A2.

All AEs reported during the Phase 3 studies were assessed by the Investigators for a relationship to the study treatment (i.e. not related or related). The most commonly reported related AEs (≥1% of subjects in the total aducanumab group) by PT in Pool A1 are presented in Table 40.

Table 40: Most commonly reported (⩾1% in the total aducanumab group) related AEs by PT – Pool A1

Preferred term	Placebo N = 1087	Aducanumab 3 mg/kg (N=760)	Aducanumab 6 mg/kg (N=405)	Aducanumab 10 mg/kg (N=1033)	Aducanumab total (N=2198)
Subjects with any event	273 (25.1)	373 (49.1)	148 (36.5)	530 (51.3)	1051 (47.8)
Headache	46 (4.2)	66 (8.7)	22 (5.4)	92 (8.9)	180 (8.2)
Dizziness	21 (1.9)	20 (2.6)	6 (1.5)	30 (2.9)	56 (2.5)
Nausea	11 (1.0)	9 (1.2)	4 (1.0)	17 (1.6)	30 (1.4)
Fatigue	22 (2.0)	14 (1.8	5 (1.2)	23 (2.2)	42 (1.9)
Confusional state	5 (0.5)	13 (1.7)	4 (1.0)	23 (2.2	40 (1.8)
MRI abnormalities					
Amyloid related imaging abnormality-oedema/effusion	28 (2.6)	222 (29.2)	83 (20.5)	362 (35.0)	667 (30.3)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	58 (5.3)	133 (17.5)	48 (11.9)	180 (17.4)	361 (16.4)
Superficial siderosis of central nervous system	21 (1.9)	88 (11.6)	22 (5.4)	143 (13.8)	253 (11.5)

2.5.7.3. Serious adverse event/deaths/other significant events

Serious adverse events

The incidence of serious adverse events per SOC in Pool A1 is presented in Table 41. The most commonly reported serious adverse events were fall (placebo n=18 [1.7%], aducanumab n=29 [1.3%], ARIA-E

(placebo n=1 [<0.1%], aducanumab n=22 [1.0%]), syncope (placebo n=5 [0.5%], aducanumab n=15 [0.7%]) and ARIA-H (placebo n=0, aducanumab n=8 [0.4%]).

There were more syncope PT SAEs cases reported in the aducanumab group compared to placebo. In addition, SAEs of PT presyncope were identified in 3 patients (0.1%) treated with aducanumab and none in placebo group. Similarly, subdural haematoma (0.3%, n=6) was reported in aducanumab treated patients vs one case (<0.1%) in the placebo group. The relationship of these adverse events and falls is unclear.

Table 41: Serious adverse events – Pool A1

System Organ Class	Placebo N = 1087	Aducanumab 3 mg/kg (N=760)	Aducanumab 6 mg/kg (N=405)	Aducanumab 10 mg/kg (N=1033)	Aducanumab total (N=2198)
Subjects with any event	151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
Nervous system disorders	32 (2.9)	23 (3.0)	11 (2.7)	38 (3.7)	72 (3.3)
Injury, poisoning and procedural complications	28 (2.6)	22 (2.9)	11 (2.7)	17 (1.6)	50 (2.3)
Gastrointestinal disorders	16 (1.5)	16 (2.1)	2 (0.5)	21 (2.0)	39 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	17 (1.6)	13 (1.7)	13 (3.2)	13 (1.3)	39 (1.8)
Infections and infestations	17 (1.6)	9 (1.2)	7 (1.7)	20 (1.9)	36 (1.6)
Cardiac disorders	25 (2.3)	9 (1.2)	8 (2.0)	13 (1.3)	30 (1.4)
Musculoskeletal and connective tissue disorders	5 (0.5)	7 (0.9)	5 (1.2	5 (0.5)	17 (0.8)
Psychiatric disorders	12 (1.1)	5 (0.7)	2 (0.5)	8 (0.8)	15 (0.7)
Vascular disorders	10 (0.9)	2 (0.3)	3 (0.7)	8 (0.8)	13 (0.6)
Respiratory, thoracic and mediastinal disorders	9 (0.8)	1 (0.1)	2 (0.5)	9 (0.9)	12 (0.5)
General disorders and administration site conditions	12 (1.1)	4 (0.5)	1 (0.2)	6 (0.6)	11 (0.5)
Metabolism and nutrition disorders	4 (0.4)	3 (0.4)	2 (0.5)	1 (<0.1)	6 (0.3)
Renal and urinary disorders	3 (0.3)	2 (0.3)	0	4 (0.4)	6 (0.3)
Reproductive system and breast disorders	1 (<0.1)	2 (0.3)	0	4 (0.4)	6 (0.3)

Hepatobiliary disorders	4 (0.4)	1 (0.1)	0	4 (0.4)	5 (0.2)
Eye disorders	3 (0.3)	0	0	3 (0.3)	3 (0.1)
Ear and labyrinth disorders	2 (0.2)	1 (0.1)	0	1 (<0.1)	2 (<0.1)
Congenital, familial and genetic disorders	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)
Endocrine disorders	0	1 (0.1)	0	0	1 (<0.1)
Investigations	2 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Skin and subcutaneous tissue disorders	0	1 (0.1)	0	0	1 (<0.1)
Blood and lymphatic system disorders	1 (<0.1)	0	0	0	0

The incidence of serious adverse events in the total aducanumab group in Pool A2 was 16.2%. The most common serious adverse events were fall (total aducanumab 1.8%), ARIA-E (total aducanumab 1.0%) and syncope (total aducanumab 0.8%).

Deaths

A total of 31 deaths were reported in the aducanumab clinical development programme while participants were enrolled in clinical studies (placebo: 6; aducanumab: 25), see Table 42. The incidence of death in both groups was 0.5%. 24 of these deaths (placebo: 5; aducanumab: 19) occurred during Phase 3 Studies 301 and 302. With the exception of 1 participant in Study 103 who died due to an intracranial haemorrhage, none of the causes of death was assessed by the Investigator as related to study treatment. All five deaths in the placebo group appeared to occur in the 302 study and none in the 301 study. The reasons for this disbalance are unclear.

Table 42: Subjects who died during aducanumab studies

Aducanumab Dose/ ApoE ε4 Status/ Study/ Study period		Adverse event	Relevant Comorbidities/ Medical History[1]
Aducanumab-Treated			
<10 mg/kg ApoE ε4 Noncarrier 221AD301/LTE		Respiratory failure	Hypertension Sleep apnoea Coronary artery disease Advanced dementia
10 mg/kg ApoE ε4 Carrier 221AD301/LTE		Myocardial infarction	Hypertension Cardiovascular disorder
<10 mg/kg ApoE ε4 Carrier 221AD301/ PC		Cerebrovascular accident	Hypertension
<10 mg/kg ApoE ε4 Carrier 221AD301/ PC		Cardiac arrest	Hyperlipidaemia Hypertension Coronary artery disease

Aducanumab Dose/ ApoE ε4 Status/ Study/ Study period		Adverse event	Relevant Comorbidities/ Medical History[1]
<10 mg/kg ApoE ε4 Carrier 221AD301/ PC		Dystonia	Dementia with Lewy bodies[2]
<10 mg/kg ApoE ε4 Noncarrier 221AD301/ LTE		Dementia Alzheimer's type	Hallucinations Alcohol use
10 mg/kg ApoE ε4 Carrier 221AD301/ PC			No relevant medical history
10 mg/kg ApoE ε4 Carrier 221AD301/ LTE		Pneumonia	Hypertension Atrial fibrillation Dysphagia Mitral valve disease
10 mg/kg ApoE ε4 Noncarrier 221AD301/ PC		Lung neoplasm malignant	No relevant medical history
10 mg/kg ApoE ε4 Noncarrier 221AD301/ LTE		Dementia Alzheimer's type	Depression HTN Bronchiectasis
<10 mg/kg ApoE ε4 Carrier 221AD302/ LTE		Dementia Alzheimer's type	Coronary artery disease Dyslipidaemia Hypertension Renal failure Transient ischaemic attack Former smoker
<10 mg/kg ApoE ε4 Noncarrier 221AD302/ LTE		Pulmonary sepsis Pneumonia aspiration	LDL increased
<10 mg/kg ApoE ε4 Noncarrier 221AD302/ LTE		Cholangiocarcinoma	Hypertension
10 mg/kg ApoE ε4 Carrier 221AD302/ PC		Cerebellar infarction Cerebellar infarction Lacunar infarction	Dyslipidaemia Breast cancer
10 mg/kg ApoE ε4 Carrier 221AD302/ PC		Pulmonary embolism	Hypercholesterolaemia Hypertension Systemic lupus erythematosus Pancreatic carcinoma metastatic[2]
10 mg/kg ApoE ε4 Carrier 221AD302/ PC		Cardiac arrest Renal failure	Arteriosclerosis Hyperlipidaemia Type 2 diabetes
10 mg/kg ApoE ε4 Carrier 221AD302/ PC		Myocardial infarction	Coronary artery disease Hypercholesterolaemia Sleep apnoea

Aducanumab Dose/ ApoE ε4 Status/ Study/ Study period		Adverse event	Relevant Comorbidities/ Medical History[1]
10 mg/kg ApoE ε4 Noncarrier 221AD302/ PC		Pleural mesothelioma	Emphysema Hypertension
10 mg/kg ApoE ε4 Noncarrier 221AD302/ PC		Cardiac arrest	Hypercholesterolaemia Hypertension Former smoker
<10 mg/kg ApoE ε4 Noncarrier 221AD103/ LTE		Dementia Alzheimer's type	Coronary artery disease Depression Hypertension
<10 mg/kg ApoE ε4 Carrier 221AD103/ LTE		Cerebral haemorrhage	Lacunar infarct
10 mg/kg ApoE ε4 Carrier 221AD103/PC		Cerebrovascular accident	Hypertension Hyperlipidaemia Sleep apnoea Tobacco use
<10 mg/kg ApoE ε4 Carrier 221AD103/LTE		Dementia Alzheimer's type	Depressed mood
<10 mg/kg/ ApoE ε4 Carrier 221AD103/LTE		Myocardial infarction	Coronary artery disease Hyperlipidaemia Chronic kidney disease
10 mg/kg ApoE ε4 Noncarrier 221AD103/LTE		Abdominal pain, Arteriosclerosis coronary artery, Urinary retention	Hypertension Coronary artery disease Hypercholesterolaemia
Placebo			
Placebo ApoE ε4 Carrier 221AD302/PC		Urosepsis	Hypertension Type 2 diabetes Hypercholesterolaemia
Placebo ApoE ε4 Noncarrier 221AD302/PC		Cardiac failure congestive	Coronary artery disease Chronic kidney disease Hypertension Hyperlipidaemia Sleep apnoea
Placebo ApoE ε4 Noncarrier/ 221AD302/PC		Cardiac failure congestive	Atrial fibrillation Hypertension
Placebo ApoE ε4 Carrier 221AD302/PC		Myocardial infarction	Hypercholesterolaemia Hypertension
Placebo ApoE ε4 Noncarrier 221AD302/PC		Death	Former tobacco user Lung adenocarcinoma stage IV[2] Hypertension

Aducanumab Dose/ ApoE ε4 Status/ Study/ Study period		Adverse event	Relevant Comorbidities/ Medical History[1]
Placebo ApoE ε4 Carrier 221AD103/PC		Cardiac arrest	Hypertension Left and right bundle branch blocks

2.5.7.4. Adverse Events of special interest

ARIA

Amyloid-related imaging abnormalities have been reported in an increased incidence in subjects receiving anti-Aβ monoclonal antibodies and were therefore adverse events of specific interest also for aducanumab.

ARIA monitoring and managing plan were set up for the aducanumab clinical program.

ARIA monitoring

In the pivotal studies 301 and 302, brain MRIs for ARIA monitoring during the placebo-controlled phase was performed as presented in Figure 39. If ARIA was detected, the information collected included the type of ARIA detected, the radiographic severity of the finding, location in the brain, and the status of the finding as compared with the prior MRI. The radiographic severity of ARIA-E and ARIA-H was graded based on focality and extent of involvement, as shown in Table 43. all ARIA findings detected on MRI were to be reported as AEs by Investigators. Additionally, the Investigator assessed whether the ARIA finding on MRI was symptomatic or asymptomatic, and this assessment was based on the Investigator's clinical judgement. Symptoms, if any, were separately reported as AEs.

Figure 39: MRI Monitoring During the Placebo-Controlled Period of the Phase 3 Studies 301 and 302

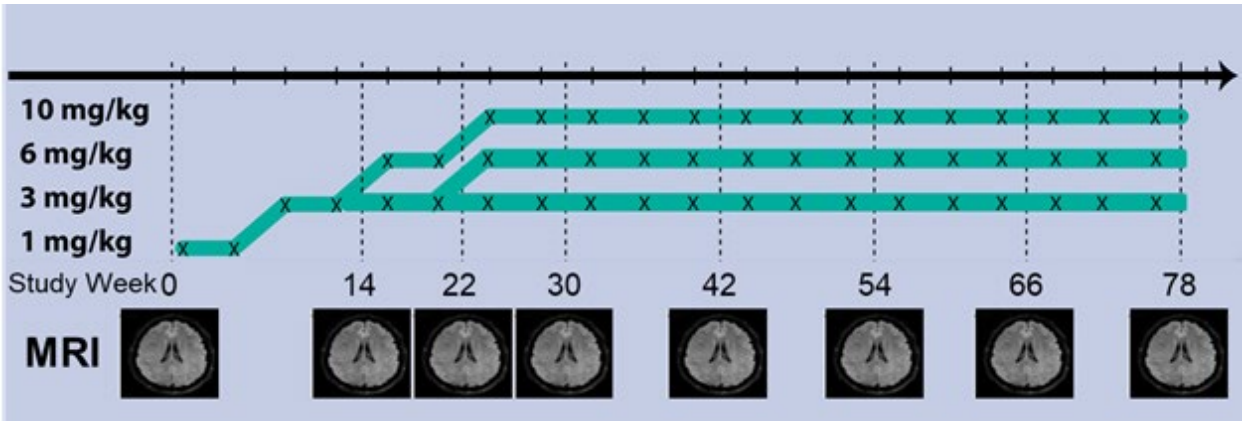


Table 43: Severity of ARIA-E and ARIA-H on MRI

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhaemorrhage	≤ 4 new incident microhaemorrhages	5 to 9 new incident microhaemorrhages	10 or more new incident microhaemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

ARIA management

Guidelines included the criteria for dosing to be continued, suspended and then resumed, or permanently discontinued due to ARIA findings. The criteria were based on the type(s) of ARIA findings detected (ARIA-E and/or ARIA-H microhaemorrhage, superficial siderosis, macrohaemorrhage), the radiographic severity of the ARIA findings (as assessed by the central MRI reader), whether a participant had any clinical symptoms, and, if symptoms were present, their clinical severity. The criteria for ARIA management evolved during the aducanumab clinical program based on ARIA observations throughout the studies from a very cautious to a more lenient approach.

Incidence of ARIA

The incidence of ARIA in Pool A1 and Pool A2 is presented in Table 44. The safety MRI population includes all randomised participants who received at least 1 dose of study treatment and had at least 1 postbaseline MRI assessment.

Table 44: ARIA Events Based on AE eCRF - Pool A1 and Pool A2 Safety MRI Population

	Placebo N = 1076	Aducanumab 3 mg/kg (N=756)	Aducanumab 6 mg/kg (N=392)	Aducanumab 10 mg/kg (N=1029)	Aducanumab total (N=2177)
Pool A1					
Number of subjects with ARIA-E	29 (2.7)	223 (29.5)	83 (21.2)	362 (35.2)	668 (30.7)
Number of subjects with ARIA-H	94 (8.7)	193 (25.5)	63 (16.1)	291 (28.3)	547 (25.1)
ARIA-H microhemorrhage	71 (6.6)	141 (18.7)	50 (12.8)	197 (19.1)	388 (17.8)
ARIA-H macrohemorrhage	4 (0.4)	1 (0.1)	3 (0.8)	3 (0.3)	7 (0.3)
ARIA-H superficial siderosis	24 (2.2)	91 (12.0)	23 (5.9)	151 (14.7)	265 (12.2)

ARIA-E and ARIA-H	12 (1.1)	142 (18.8)	42 (10.7)	228 (22.2)	412 (18.9)
Concurrent ARIA-E and ARIA-H	12 (1.1)	135 (17.9)	39 (9.9)	216 (21.0)	390 (17.9)
ARIA-E or ARIA-H	111(10.3)	274 (36.2)	104 (26.5)	425 (41.3)	803 (36.9)
Isolated ARIA-E	17 (1.6)	81 (10.7)	41 (10.5)	134 (13.0)	256 (11.8)
Isolated ARIA-H	82 (7.6)	51 (6.7)	21 (5.4)	63 (6.1)	135 (6.2)
Pool A2		N=946	N=441	N=1335	N=2722
Number of subjects with ARIA-E		274 (29.0)	91 (20.6)	455 (34.1)	820 (30.1)
Number of subjects with ARIA-H		262 (27.7)	69 (15.6)	379 (28.4)	710 (26.1)
ARIA-H microhemorrhage		194 (20.5)	57 (12.9)	250 (18.7)	501 (18.4)
ARIA-H macrohemorrhage		2 (0.2)	3 (0.7)	5 (0.4)	10 (0.4)
ARIA-H superficial siderosis		124 (13.1)	25 (5.7)	201 (15.1)	350 (12.9)
ARIA-E and ARIA-H		183 (19.3)	45 (10.2)	289 (21.6)	517 (19.0)
Concurrent ARIA-E and ARIA-H		172 (18.2)	43 (9.8)	272 (20.4)	487 (17.9)
ARIA-E or ARIA-H		353 (37.3)	115 (26.1)	545 (40.8)	1013 (37.2)
Isolated ARIA-E		91 (9.6)	46 (10.4)	166 (12.4)	303 (11.1)
Isolated ARIA-H		79 (8.4)	24 (5.4)	90 (6.7)	193 (7.1)

NOTE 1: ARIA-E, ARIA-H microhemorrhage and ARIA-H superficial siderosis are identified based on preferred term (MedDRA 22.0). ARIA-H macrohemorrhage is identified based on eCRF reported term.
NOTE 2: Concurrent is defined as overlapping in MRI duration of 2 ARIA events.
NOTE 3: ARIA-E is defined as isolated if the subject experienced no ARIA-H during the placebo-controlled period. ARIA-H is isolated if subject experienced no ARIA-E during the placebo-controlled period.

In addition to aducanumab dose, the incidence of ARIA was dependent on ApoE ε4 status, with a higher incidence in ApoE ε4 carriers compared to noncarriers. Incidence of ARIA-E in the total aducanumab group was 36.0% in the carriers as compared to 19.1% in the non-carriers. Within ApoE ε4 carriers, the incidence of ARIA-E was higher among ApoE ε4 homozygotes (total aducanumab group: 55.1%) compared to ApoE ε4 heterozygotes (total aducanumab group: 29.6%). Incidence of ARIA-H in the total aducanumab group was 21.7% in the carriers as compared to 12.6% in the non-carriers.

Radiographic severity, symptomatic status, and clinical symptom severity of ARIA

The maximum severity and worst symptomatic status among subjects with ARIA in Pool A1 are presented in Table 45.

Table 45: The maximum severity and worst symptomatic status among subjects with ARIA in Pool A1

	Placebo N = 1076	Aducanumab 3 mg/kg (N=756)	Aducanumab 6 mg/kg (N=392)	Aducanumab 10 mg/kg (N=1029)	Aducanumab total (N=2177)
Number of subjects with ARIA	111	274	104	425	803
Maximum MRI severity[a]					
Mild	94 (84.7)	102 (37.2)	49 (47.1)	158 (37.2)	309 (38.5)
Moderate	13 (11.7)	120 (43.8)	39 (37.5)	186 (43.8)	345 (43.0)
Severe	4 (3.6)	52 (19.0)	16 (15.4)	81 (19.1)	149 (18.6)
Worst symptomatic status[b]					
Asymptomatic	106 (95.5)	218 (79.6)	87 (83.7)	322 (75.8)	627 (78.1)
Symptomatic	5 (4.5)	56 (20.4)	17 (16.3)	103 (24.2)	176 (21.9)
Maximum symptom severity[c]					
Mild symptoms	3 (2.7)	33 (12.0)	12 (11.5)	67 (15.8)	112 (13.9)
Moderate symptoms	1 (0.9)	16 (5.8)	3 (2.9)	28 (6.6)	47 (5.9)
Severe symptoms	1 (0.9)	4 (1.5)	2 (1.9)	4 (0.9)	10 (1.2)
Discontinued treatment due to ARIA	6 (5.4)	47 (17.2)	21 (20.2)	64 (15.1)	132 (16.4)

(a) The maximum MRI severity across all the events of the type of ARIA being analyzed for each subject.
(b) The worst symptomatic status across all the events of the type of ARIA being analyzed for each subject.
(c) The maximum symptom severity across all the symptomatic events of the type of ARIA being analyzed for each subject.

The results with respect to MRI severity and symptoms were similar in Pool A2. Based on analysis of Pool A2 data, both the incidence of symptomatic ARIA and increase in clinical symptoms severity increased with increasing MRI severity.

Most common and severe symptoms of symptomatic ARIA

Table 46 presents ARIA-related AEs occurring in at least 5 participants in the total aducanumab group in Pool A1.

Table 46: ARIA-Related Adverse Events Among Subjects With Symptomatic ARIA by System Organ Class and Preferred Term occurring in in at least 5 participants in the total aducanumab group - Pool A1 Safety MRI Population

	Placebo N = 1076	Aducanumab 3 mg/kg (N=756)	Aducanumab 6 mg/kg (N=392)	Aducanumab 10 mg/kg (N=1029)	Aducanumab total (N=2177)
Number of subjects with symptomatic ARIA	5	56	17	103	176
Headache	3 (60.0)	32 (57.1)	9 (52.9)	48 (46.6)	89 (50.6)
Confusional state	1 (20.0)	9 (16.1)	3 (17.6)	15 (14.6)	27 (15.3)
Dizziness	0	5 (8.9)	2 (11.8)	11 (10.7)	18 (10.2)
Nausea	0	3 (5.4)	1 (5.9)	8 (7.8)	12 (6.8)
Fatigue	0	3 (5.4)	1 (5.9)	5 (4.9)	9 (5.1)
Gait disturbance	0	1 (1.8)	1 (5.9)	5 (4.9)	7 (4.0)
Vision blurred	0	1 (1.8)	0	5 (4.9)	6 (3.4)
Visual impairment	0	1 (1.8)	0	5 (4.9)	6 (3.4)
Fall	0	3 (5.4)	0	3 (2.9)	6 (3.4)
Balance disorder	0	1 (1.8)	2 (11.8)	2 (1.9)	5 (2.8)
Memory impairment	0	1 (1.8)	0	4 (3.9)	5 (2.8)
Disorientation	0	1 (1.8)	1 (5.9)	3 (2.9)	5 (2.8)
Vertigo	0	1 (1.8	0	0 4 (3.9)	5 (2.8)

NOTE 1: A subject was counted only once within each system organ class and preferred term (MedDRA version 22.0).
NOTE 2: Percentages are based on the number of subjects with symptomatic ARIA.

In Pool A2, the most common ARIA-related adverse events in patients with symptomatic ARIA were similar to those in Pool A1, with the addition of aphasia and visual field defect (both 2.2% in total aducanumab group).

Serious ARIA

The incidence of ARIA considered serious by the investigator is reported in Table 47. The results on Pool A2 were similar.

Table 47: Incidence of serious ARIA - Pool A1 safety MRI population

	Placebo (N=1076)	Aducanumab 3 mg/kg (N=756)	Aducanumab 6 mg/kg (N=392)	Aducanumab 10 mg/kg (N=1029)	Aducanumab total (N=2177)
Number of subjects with serious ARIA-E event	1 (<0.1)	6 (0.8)	3 (0.8)	13 (1.3)	22 (1.0)
Serious ARIA-E related to study drug[a]	1 (<0.1)	6 (0.8)	3 (0.8)	13 (1.3)	22 (1.0)
Serious symptomatic ARIA-E	0	6 (0.8)	2 (0.5)	12 (1.2)	20 (0.9)
Number of subjects with serious ARIA-H microhaemorrhage event	0	4 (0.5)	1 (0.3)	3 (0.3)	8 (0.4)
Serious ARIA-H microhemorrhage related to study drug[a]	0	4 (0.5)	1 (0.3)	3 (0.3)	8 (0.4)
Serious symptomatic ARIA-H microhemorrhage	0	3 (0.4)	1 (0.3)	3 (0.3)	7 (0.3)
Number of subjects with serious ARIA-H macrohaemorrhage event	1(<0.1)	0	0	1 (<0.1)	1 (<0.1)
Serious ARIA-H macrohemorrhage related to study drug[a]	1(<0.1)	0	0	1 (<0.1)	1 (<0.1)
Serious symptomatic ARIA-H macrohemorrhage	0	0	0	1 (<0.1)	1 (<0.1)
Number of subjects with serious ARIA-H superficial siderosis event	0	1 (0.1)	0	5 (0.5)	6 (0.3)
Serious ARIA-H superficial siderosis related to study drug[a]	0	1 (0.1)	0	5 (0.5)	6 (0.3)
Serious symptomatic ARIA-H superficial siderosis	0	1 (0.1	0	2 (0.2)	3 (0.1)

Recurrent ARIA

From those patients in the aducanumab total group in Pool A1 who had ARIA-E and at least one dose one MRI after first ARIA-E resolution, 36.8% experienced a second ARIA-E event. The characteristics of the second event were similar to the first event in terms of MRI severity, symptomatic status and severity of symptoms. The majority of events (97.9% in the total aducanumab group) resolved and as with the

first event, in the majority of patients, treatment was continued as planned or suspended and then continued as planned.

Most aducanumab-treated patients who had asymptomatic first ARIA-E event had also an asymptomatic second event (95.1%). In terms of MRI severity, most patients who had mild or moderate severity first ARIA-E event experienced the same category second event.

2.5.7.5. Laboratory findings

No relevant trends were observed for any of the haematology parameters (white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, basophils, red blood cells) in the placebo or aducanumab groups in Pool A1. Potentially clinically significant blood chemistry results were reported infrequently and for similar proportions of participants in the placebo and aducanumab groups

In all treatment groups, liver enzyme abnormalities were infrequent, and no notable differences were observed between the placebo and aducanumab groups in Pool A1. The majority (>90%) of ALT, AST, total bilirubin, and ALP maximum post-baseline values were ≤ 1 × ULN.

Two participants in Pool A1 (1 participant in the placebo and 1 participant in the 6 mg/kg group) were identified with liver enzyme values that met biochemical criteria for Hy's law (ALT or AST > 3 × ULN, total bilirubin > 2 × ULN). These were considered not related to the study treatment.

No notable trends were observed for any of the urinalysis parameters in the placebo or aducanumab groups in Pool A1. Potentially clinically significant urinalysis abnormalities did not occur at an incidence of more than 3% in any treatment group.

Vital signs

The overall incidence of AEs in the Investigations SOC related to changes in vital signs was low and similar across all treatment groups. The only vital sign AEs reported in more than 1% of participants in the placebo or total aducanumab groups was weight decreased (placebo: 1.7%; aducanumab: 2.0%).

A slightly higher proportion of patients treated with aducanumab reported SBP increase >160 mmHg (13.2%) compared to placebo (11.4%) in pool A1. At the same time, a slightly higher proportion of patients treated with aducanumab reported DBP increase >90 mmHg (18.9%) compared to placebo (17.9%) in pool A1. Similarly, higher proportion of SBP increase >160 mmHg (13.8%) and DBP increase >90 mmHg (20.4%) was also reported in pool A2.

While a rather similar proportion of patients treated with aducanumab (12.9%) and placebo (12.4%) reported weight decrease in pool A1, it was a further higher proportion of patients treated with aducanumab reporting weight decrease (16.5%) in pool A2, including long term open-label extension.

2.5.7.6. In vitro biomarker test for patient selection for safety

The Phase 3 studies enrolled participants ranging in age from 50 to 85 years. The overall incidence of adverse events occurring in the total aducanumab group was similar between the analysed age groups ≤ 64, 65 to 74, and ≥ 75 years in Pool A1, see Table 48. Serious adverse events occurred in higher frequency in the older age group; the pattern and incidence were similar to the placebo group. In terms of ARIA-E, the incidence was higher in patients in the lowest age group.

Table 48: Incidence of (serious) adverse events, deaths and relevant specific adverse events in the total aducanumab group in Pool A1 by age group

MedDRA Terms	**Age <65 number (percentage)** N=461	**Age 65-74 number (percentage)** N=1041	**Age 75> number (percentage)** N=696
Total AEs	415 (90.0%)	947 (91.0)	631 (90.7)
Serious AEs – Total	39 (8.5)	134 (12.9)	127 (18.2)
Deaths	1 (0.2)	3 (0.3)	7 (1.0)
AE leading to drop-out	16 (3.5)	43 (4.1)	38 (5.5)
ARIA-E	150 (32.5)	332 (31.9)	186 (26.7)
ARIA-H	74 (16.1)	190 (18.3)	124 (17.8)
Fall	38 (8.2)	149 (14.3)	123 (17.7)
Superficial siderosis	52 (11.3)	140 (13.4)	73 (10.5)

2.5.7.7. Immunological events

Summary of immunogenicity in Pool A1 is presented in

Table **49**.

Table 49: Summary of Immunogenicity – Pool A1

	Placebo (N=1069)	Aducanumab 3 mg/kg (N=750)	Aducanumab 6 mg/kg (N=388)	Aducanumab 10 mg/kg (N=1013)	Aducanumab total (N=2151)
Number of subjects with treatment-emergent anti-aducanumab antibody positive response	2 (0.2)	4 (0.5)	3 (0.8)	3 (0.3)	10 (0.5)
Number of subjects with treatment-emergent anti-aducanumab antibody positive response at					
Week 24	2/1044	3/708 (0.4)	2/365 (0.5)	1/967 (0.1)	6/2040 (0.3)
Week 32	2/663	0/453	1/200 (0.5)	0/634	1/1287 (<0.1)
Week 56	1/980	0/672	1/327 (0.3)	1/906 (0.1)	2/1905 (0.1)
Week 78	0/793	0/569	0/281	0/742	0/1592
Week 80	0/538	1/367 (0.3)	0/189	0/436	1/992 (0.1)

NOTE 1: Entries are number of subjects with antibody positive response/number at risk (percentages). Number at risk at a specific visit is the number of subjects with an antibody value at the specific visit. Subjects must have at least one post-baseline evaluable assessment to be included in the table.

In Pool A2, 37 participants (1.4%) were positive for anti-aducanumab antibodies at any time during the aducanumab-treated period of the study. Of these, 15 participants were treatment-emergent (0.6%).

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

In Pool A1, approximately 60% of participants were taking concomitant symptomatic Alzheimer's disease medication during the placebo-controlled phase of the pivotal studies. There were no significant differences in adverse events between these groups.

In Pool A1, 37.1% of aducanumab-treated participants and 33.8% of placebo participants were taking any concomitant aspirin-containing medication during the placebo-controlled period of the Phase 3 studies.

The incidence of ARIA-H in the total aducanumab group was similar in patients taking aspirin or aspirin-containing medication or non-aspirin anticoagulants and patients not taking these medications. The incidence of radiographically severe ARIA-H was somewhat higher in the patients taking concomitant aspirin or aspirin containing medications as compared to those who did not use these medications: 6.1% vs. 4.4%.

2.5.7.9. Discontinuation due to adverse events

In Pool A1, the overall incidence of AEs that led to discontinuation of study treatment was higher in the total aducanumab group (9.1%) than the placebo group (4.1%). The higher incidence of treatment discontinuation was largely due to the increased incidence of ARIA events, including ARIA-H microhaemorrhage (placebo: 0; aducanumab: 2.4%) ARIA-H superficial siderosis (placebo: 0.2%; aducanumab: 2.3%), and ARIA-E (placebo: < 0.1%; aducanumab: 1.3%).

In Pool A1 the incidence of AEs that resulted in withdrawal from the study was higher in the total aducanumab group (4.4%) than the placebo group (2.9%). AEs in the total aducanumab group that led to study withdrawal with an incidence ≥ 0.5% were ARIA-H superficial siderosis (placebo: 0; aducanumab: 0.7%), ARIA-H microhaemorrhage (placebo: 0; aducanumab: 0.6%), and ARIA-E (placebo: < 0.1%; aducanumab: 0.5%). Cardiac arrest (placebo: 0; aducanumab: 0.1%) was the only other AE that led to withdrawal in at least 3 (0.1%) aducanumab-treated participants.

2.5.7.10. Late-breaking safety information

On 7 October 2021, the applicant informed the EMA of a fatal event in study 221AD304 (EMBARK). The applicant is collecting additional data on this case, however initial information has been submitted.

Biogen received the initial safety report with the event "severe cerebral edema". Biogen received an update for the event which included a change of the event term "severe cerebral edema" to the event term to "ARIA-E", and a report that the event outcome was fatal.

The participant was a 75 year-old woman with a past medical history of hypertension, dyslipidemia, and polymyalgia rheumatica who had received 10 doses of aducanumab in Study 221AD304. Starting 8 days after the last dose, she experienced convulsions and was hospitalized. Hospital records report preceding symptoms of confusion and speech difficulty. These symptoms were noted to have an onset date one month prior to hospitalization. Head CT and MRI were reported as showing severe cerebral edema. During her hospitalization seizure activity persisted for several days, but was controlled i.e. EEG showed "no epileptic activity'. Hospital records note recurrence of seizure activity requiring multiple anti-epileptic medications and an ICU admission. She was transferred to another hospital for specialized care. The participant was subsequently reported to have died 40 days after initial hospitalisation. The reporting

investigator suspects that the death was related to status epilepticus secondary to ARIA-E, however he was not involved in the patient's hospital care and has requested hospital records.

The cause of death remains under investigation (*see section below)*, pending the death certificate and hospital records from the 9 days prior to patient's death.

2.5.8. Discussion on clinical safety

The aducanumab clinical development programme includes seven clinical studies in Alzheimer's disease and one clinical study in healthy volunteers. Throughout the aducanumab clinical development program for Alzheimer's disease, 3078 subjects received at least one dose of aducanumab. The main body of evidence for aducanumab safety originates from the two Phase 3 placebo-controlled clinical studies 221AD301 and 221AD302. Within this safety pool (Pool A1), a total of 2959 patients were exposed to aducanumab, of whom 1948 patients for at least 1 year. Long-term safety data gathered in ongoing study 304 is necessary to characterise the safety profile concerning recurrent ARIA.

Amyloid-related imaging abnormalities (ARIAs) induced by anti-Aβ monoclonal antibodies have been reported in subjects receiving these medications and were therefore adverse events of specific interest also for aducanumab. A monitoring and management plan for ARIAs was set up for the clinical trials, which evolved from a very cautious to a more lenient approach. The ARIA severity scoring system used in the studies has been developed by Alzheimer's Association Research Roundtable Workgroup experts and has been used in several clinical trials examining amyloid-modifying therapeutics.

Keeping in mind that ARIA is a known AE widely discussed in the literature describing treatment effects of amyloid targeting antibodies in AD patients as well as information provided in the ICF, additional MRI investigations performed due to ARIA could potentially affect patients and caregivers and reporting of AEs. The Applicant expressed the belief that functional unblinding of patients and caregivers do not affect reporting of AEs.

Indeed, the observed adverse events in the provided data are dominated by the treatment dependent ARIA-E and ARIA-H and symptoms associated with these. SOC nervous system disorders were also the only SOC clearly separating from placebo, the incidence of adverse events in the total aducanumab group was 58.5% vs 42.3% in the placebo group. From the list of most commonly reported adverse events, the applicant has chosen to present hypersensitivity, ARIA-E, ARIA-H microhaemorrhage, ARIA-H superficial siderosis, headache, confusional state, diarrhoea and fall in the SmPC section 4.8, based on an assessment of probable causality. This was agreed. The applicant was also requested to add subdural hematoma to the list of adverse events based on disbalance in the incidence of subdural hematoma between the treatment groups in Pool A1 safety MRI population. However, the applicant has clarified that when grouping PTs subdural hematoma and subdural haemorrhage together, which in fact represent the same radiographic finding, the incidence is balanced between the groups: 0.4% in the placebo group (4/1076) and 0.5% in the total aducanumab group (11/2177) in the Pool A1 safety MRI population. The incidence rate per 100-subject years in this pool was 0.3 in the placebo group and 0.4 in the total aducanumab group. There are some differences seen in the characteristics of cases between the groups, even if the incidence is comparable. However, the low number of cases in the placebo group hampers any conclusions based on these observations. Therefore, considering that the incidence is balanced and that the risk of subdural hematoma is higher in these patients as compared to healthy adult population, it is accepted that subdural hematoma was not to be included in the SmPC as a treatment related adverse event and to the RMP as an important identified risk. With respect to falls, the applicant discussed the link to dizziness. The incidence of falls was higher in the aducanumab treated subjects as compared to patients in the placebo group. This difference remained irrespective of whether the patient also reported

dizziness. Therefore, it was agreed with the applicant that fall is added as an independent ADR in the SmPC.

In Pool A1, 10% of patients did not receive their assigned target dose of 10 mg/kg, and 14.9% of patients did not receive their assigned target dose of 6 mg/kg. The applicant had clarified that the most common reason for this was simply discontinuing the study before the target dose was reached. The most common reason for discontinuation was an adverse event. Of participants who did not reach the assigned target dose despite receiving 7 or more infusions, the vast majority had up-titration temporarily interrupted or permanently stopped due to ARIA, as was required by the study protocol.

The overall incidence of related serious adverse events was 1.7% in the total aducanumab group as compared to 0.7% in the placebo group and dominated by ARIAs. The incidence of death was 0.5% in the aducanumab and placebo group in Pool A1; however, it was noted that there were no deaths occurring due to CNS adverse events in the placebo group while four occurred in the aducanumab group. The applicant provided a further discussion on these cases; it is agreed that a definite causal relationship to aducanumab cannot be concluded due to confounding factors such as risk factors for ischaemic cerebrovascular disease.

Also, all five deaths in the placebo group appeared to occur in the 302 study and none in the 301 study. The applicant has explored the potential differences in baseline characteristics that may have contributed to this. There are some differences which may have played a part, e.g. higher age or lower use of cardiovascular prophylactic treatment in study 302. However the differences are small and their impact remains speculative. Reasons for the difference between the studies in deaths occurring in the placebo group cannot be confirmed.

In addition, one death due to cerebral haemorrhage was considered related to aducanumab by the investigator, which was later challenged via re-review of MRIs. It is possible, however, that aducanumab may have aggravated the existing neurovascular pathology. The applicant has provided a detailed description of the death. A thorough discussion on aducanumab possibly aggravating the existing neurovascular pathology is still lacking. It is nevertheless acknowledged that there are several other factors that confound the causality. Hence the contribution of aducanumab to the cerebral haemorrhage cannot be conclusively asserted nor excluded.

The late-breaking fatal case occurring in study 221AD304 is, at the time of CHMP Opinion, still insufficiently reported, and a causality assessment could not be comprehensively carried out, despite suggestive elements.

Any CNS haemorrhage was more common in aducanumab treated patients (n=19, 0.9%) compared to placebo (n=8, 0.7%) with the highest difference for subdural haematoma (n=11, 0.5%; n=2, 0.2%, respectively). Similarly, more SAE of subdural haematoma (0.3%, n=6) was reported in aducanumab treated patients vs one case (<0.1%) in the placebo group. 4 patients in the 10 mg/kg aducanumab group had cerebral haemorrhage as a cause of treatment discontinuation. As mentioned previously, subdural hematoma should be included in the list of ADRs.

Differences were observed between the two treatment groups in SAE reporting concerning a higher incidence of cardiac arrest, syncope and presyncope as well as a subdural haematoma in aducanumab treatment group. The Applicant provided a thorough discussion on confirmed 5 SAEs (3 male, 2 female) of cardiac arrest in aducanumab treated patients. Three cases of cardiac arrest were fatal. Patients age varied from 64 to 79 years old. They received 4 to 18 doses of aducanumab, and the cardiac arrest occurred 21 to 31 day after the last infusion. Most patients had a history of concomitant diseases, which included arteriosclerosis, diabetes, coronary artery disease with stent placement, chest pain, dyslipidemia, ascending aortic dissection, carotid artery stenosis, syncope and hypertension. Also, following further review of fatal cases in the placebo group, the Applicant identified 2 new cases which

might have had AE of cardiac arrest, but Investigators did not report the PT of cardiac arrest. This would make the number observed cases of cardiac arrest in the treatment groups more balanced. The common denominator of the five cases in the aducanumab group as well as two cases described in the placebo group are pre-existing serious cardiovascular conditions. It is not clear at present moment whether treatment with aducanumab have contributed to worsening of these conditions. Therefore, this is an uncertainty that would require further monitoring. It is agreed with the Applicant that available data on syncope and presyncope as discussed in response to the question is not sufficient to positively conclude on the existence of a causal relationship with aducanumab.

The appropriate monitoring and management of ARIA in clinical practice is of questionable feasibility. This is also in line with the conclusions of the SAG, which observed that the feasibility of the MRI management that appears necessary in clinical practice has been questioned, even in highly specialised centres.

In the majority of aducanumab-treated patients with ARIA, the MRI severity was mild (38.5%) or moderate (43.0%), and most patients (78.1%) were apparently asymptomatic. If there were symptoms, they were most often mild (63.6%). Also, in the majority of patients with severe ARIA-related symptoms, the symptoms resolved after treatment discontinuation. However, there are also cases in which symptoms did not resolve while on study despite treatment discontinuation. It is unknown if symptoms ultimately did or did not resolve, as no further follow-up information is available. The applicant has provided a thorough discussion on these cases, which illustrates that despite a cautious approach and early treatment suspension, severe symptoms of ARIA can remain unresolved while on study. The ultimate resolution of symptoms (or lack thereof) remains unknown. In some of these cases treatment could have been suspended earlier, or MRIs performed sooner; it is unclear why this was not followed. It remains speculative whether this would have affected the course of events. The concern regarding ARIA is shared by the experts of the SAG, who noted that ARIA-E and ARIA-H are of high clinical relevance, because of their high frequency and the potentiality of life-threatening events.

The experts also commented that the knowledge of these events (and especially of long-term consequences) is still incomplete.

In study 103 there were 5 participants (2.7% of aducanumab-treated patients) whose ARIA associated symptoms were not resolved despite drug discontinuation/suspension at the time of the symptoms or later (1 case). In all cases but one dosing was suspended or withdrawn immediately or within days, therefore a continuation of symptoms was not due to less cautious dosing action.

While the majority of ARIAs were considered asymptomatic, could have been possible that some symptoms of ARIA were masked by symptoms of Alzheimer's disease itself, e.g. confusional state or effects on cognition. To address this, the applicant provided an overview of adverse events reported in subjects with and without ARIA, an overview of adverse events reported within 4 weeks before and after reporting ARIA in those patients with ARIA as well as efficacy data (MMSE, ADAS-Cog) for patients during ARIA. The adverse event data does not bring forward any new symptoms of ARIA; based on the data, it also does not seem likely that the proportion of patients with symptomatic ARIA would be considerably underestimated. In the aducanumab 10 mg/kg group, the proportion of patients with worsening MMSE score and ADAS-Cog is similar across patients with and without ARIA, including asymptomatic patients. These data do not indicate that cognitive worsening due to ARIA would have been missed.

A further discussion was also requested on the causality to aducanumab in one case where a patient died after what seems to be a cascade of events initiating from severe ARIA-E. The cause of death of this patient was difficult to determine, although the events of cerebellar infarction and lacunar infarction were considered fatal. These were not in the same area as ARIA-E, which had stabilized at the time of cerebellar and ischaemic stroke. A causal association between aducanumab and patient's death cannot be established based on the description. The role of ARIA in the cascade of events remains unclear.

Seizures seem to occur rarely with ARIA-E. In all cases but one, seizures have resolved. Treatment with antiepileptics was stopped in all cases but one (excluding the patient who died). Therefore it seems that seizure events (possibly) related to treatment are treatable and resolve without severe sequelae in the majority of cases.

The incidence of ARIAs was almost two times higher in patients who are ApoE ε4 carriers as compared to non-carriers, i.e. 36% vs 19.1%. In Pool A1, the incidence of ARIA-E was 43.0% in ApoE ε4 carriers compared to 20.3% to in ApoE ε4 non carriers. Compared to non-carriers, ApoE ε4 carriers also had an increased incidence of ARIA H microhaemorrhage (22.7% and 12.4%, respectively) and ARIA H superficial siderosis (19.1% and 6.2%, respectively). The higher risk is likely related to the higher vascular amyloid burden in ApoE ε4 carriers as compared to the non-carriers. In addition, in ApoE ε4 carriers symptoms associated with ARIA were more often severe than in non-carriers and most serious ARIAs also occurred in ApoE ε4 carriers. Similar percentages of patients in both ApoE ε4 carriers and non-carriers developed ARIA-E related severe symptoms and discontinued treatment. Considering the fact that dosing, radiographic severity, and symptomatic status are intrinsically confounded, further examination of possible differences between ApoE ε4 carriers and non-carriers in dosing action are not considered useful. The pattern of timing of ARIAs between ApoE ε4 carrier status and genotype indicates that the majority of the first ARIA-E event in dose group 10 mg/kg (based on the proposed titration posology) occurred between weeks 12 and 44 in homozygote and heterozygote ApoE ε4 carriers and between weeks 12 and 32 in noncarriers. This slight difference is not considered relevant.

While there was no clear dose-response relationship seen in adverse events reported overall, in terms of ARIAs, the dose-relationship is evident because most ARIAs occurred in the highest 10 mg/kg dose group. This is also confirmed in the provided modelling exercise on the exposure-ARIA relationship. Dose reduction is not included in the proposed ARIA clinical management plan. There were only 26 subjects in whom the dose was reduced after the 1st ARIA-E. From these, 57.7% experienced a 2nd ARIA-E, which is a higher proportion than from patients in which dosing was continued as planned or suspended and then continued. Also, there does not seem to be a difference in recurrence between suspending treatment and then continuing or reducing the dose irrespective of whether the ARIA-E was 2nd, 3rd or etc., although the number from 3rd ARIA-E onwards are low. In conclusion, dose reduction in case of ARIA does not appear useful.

Due the ARIA monitoring and management plan guided treatment actions during the study, there are too few/no data regarding optional treatment actions in patients with severe radiographic severity and patients who were symptomatic.

For ARIA-H microhaemorrhage, recurrence was indeed higher in patients who suspended dosing as compared to those who continued. It is unclear whether there could be a mechanistical reason for this. Also, when examining patients with mild or moderate radiographic severity who were asymptomatic, differences are not seen in recurrence of ARIA-H based on dosing action taken. It should be noted that the numbers are very low in patients with moderate symptoms due to the ARIA monitoring and management plan. The same conclusions apply to ARIA-H superficial siderosis.

Based on the provided data, there are no patterns to be seen in ARIA-E or ARIA-H recurrence based on symptom severity.

The Applicant claims that - "for labelled use of aducanumab if a patient experiences new-onset symptoms, ad hoc MRI testing (distinct from the MRI monitoring plan) should be conducted if clinically indicated." Such a recommendation could be supported. The Applicant provided an updated modification of SmPC, which clarified the recommendation and stated that "if a patient experiences symptoms during an ARIA event, clinical evaluation should be conducted prior to continuing with Aduhelm dosing." This would be considered necessary, but could be insufficient as there is not enough knowledge on the potential to resolve clinical manifestations of ARIA with different courses of actions.

Discussion on recurrent ARIAs was focused on ARIA-E. While it is acknowledged that the majority of ARIA-Hs were concurrent with ARIA-E, and in many cases, treatment was discontinued after an ARIA-H event; also isolated ARIA-Hs with continuing treatment occurred. The applicant provided data on recurrent ARIA-H in the form of tables and the previously requested flow-chart. Altogether the provided data shows a rather similar pattern as was observed for ARIA-E, which is not unexpected as ARIA-E and ARIA-H were often concurrent. In the total aducanumab group, 388 patients (17.8%) had ARIA-H microhaemorrhage. Most occurred within the first 36 weeks of treatment. All but 8 stabilized, most commonly within 12 weeks. In most cases (78.9%) treatment was continued as planned, i.e. according to normal dosing schedule without dose adjustment. Of these patients, 21.1% had a second ARIA-H microhaemorrhage and 25.6% from these a third event. In terms of symptoms, the 2nd ARIA-H microhaemorrhage were often similar to the first, i.e. if the first event was asymptomatic, so was the second one. However, in terms of MRI severity, if the first event was mild, the second event was in approximately half of the cases mild (56.9%) and in half moderate or severe (43.1%). In the total aducanumab group, 265 patients (12.2%) had ARIA-H superficial siderosis. Also, most of these occurred within the first 36 weeks of treatment. All events were reported stabilized, also most commonly within 12 weeks. In 66.8% of cases, treatment was continued as planned, i.e. according to normal dosing schedule without dose adjustment. Of these patients, 24.2% had a second ARIA-H superficial siderosis and 23.4% from these a third event. In terms of symptoms, the 2nd ARIA-H superficial siderosis was often similar to the first, i.e. if the first event was asymptomatic, so was the second one. However, in terms of MRI severity, if the first event was mild, the second event was most often moderate (60.9%).

The applicant has explained that the change in MRI severity is inherent to ARIA-H, as unlike ARIA-E, ARIA-H microhaemorrhage and ARIA-H superficial siderosis are radiographic findings that typically persist on subsequent MRI scans and thus do not diminish in the MRI severity scale, e.g. from moderate to mild.

The majority of patients with an ARIA-E event experienced their first ARIA-E within 36 weeks from the first infusion. However, the distribution in time from the 1st infusion to ARIA event is somewhat different between dose groups, which is unexpected, and the 12 weeks for the subgroup analysis is considered rather long. The applicant provided a time-to-event analysis for first ARIA-E and ARIA-H. ARIA-Es and ARIA-Hs are clustered around routine MRI timing every 12 weeks as most were asymptomatic. The observed difference between the dose groups in distribution is explained by due to dose-response relationship of ARIA-E.

The incidence of ARIA-H macrohemorrhage in study 103 is much higher than in the pivotal studies, 2.7% in study 103 vs 0.4% in the Pool A2. These also include cases where the event has not completely resolved. The applicant has clarified that 3 cases in study 103 were in fact reported as ARIA-H macrohaemorrhage, similarly to the pivotal studies. This gives an incidence of 1.6% which is still larger than in the pivotal studies. However all but one of those related to aducanumab resolved with treatment discontinuation. In one case, follow-up data is not available to determine whether ARIA-H were resolved. Treatment was withdrawn in all these patients before the event of macrohaemorrhage, with previous ARIA-E or ARIA-H microhaemorrhage or superficial siderosis.

Several comments on the proposed ARIA monitoring and management plan were made during the assessment.

The Applicant initially proposed baseline MRI examination utilising a recent (within 1 year) brain MRI prior to initiation of treatment to assess for pre-treatment brain microhaemorrhages, localised superficial siderosis or brain haemorrhages > 1cm. The Applicant’s proposal for conducting a pre-treatment MRI to assess the potential presence of a contraindication was endorsed; however, having in mind the evolution of ARIA, a 1-year period as proposed for the historical MRI by the MAH was considered too long. The Applicant amended this to 6 months which was agreed.

The proposed standard MRI monitoring plan includes an MRI before treatment and 5th, 7th and 9th infusion. In approximately 30% of aducanumab-treated patients who suffered an ARIA-E, the ARIA-E was observed between 0 and 5 doses. Based on the provided data it seems that most ARIA-E cases that occurred prior to the fifth infusion occurred after the 4th infusion i.e. second 3 mg/kg dose. From patients with an ARIA-E within the first 5 infusions, radiographic severity was moderate or severe in 82.2% of patients. Most were asymptomatic and thus would not have been discovered using a symptom-triggered MRI protocol. Indeed, the majority of ARIA-E cases resolved, however in most cases, treatment was suspended as per protocol. The applicant was requested to provide further data specifically for those 41 patients who continued dosing despite ARIA-E. As expected, in patients who continued dosing as planned, many of the ARIA-Es occurring before the 5th infusion were radiographically mild and asymptomatic. From the rest of the cases where the ARIA-E was serious or symptomatic or radiographically moderate or severe, all but one patient in fact had already discontinued treatment for another reason (majority due to ARIA-H) and therefore were labelled as "Dose Not Changed". In the one patient with radiographically moderate severe ARIA-E with actual continued dosing, the ARIA-E was resolved. Thus as expected, there are hardly any data on the outcome of continued treatment with moderate or severe ARIA occurring prior to the 5th infusion.

In case of detection of a mild ARIA-E event, every 4 week monitoring is proposed. The monitoring could be stopped if ARIA-E event resolves or remain unchanged (mild) on 2 follow-up scans. It is noted that by 12 weeks, 82.2% of mild ARIA-E events resolved. However, even though the worsening, according to the Applicant, typically occurred within 8 weeks, it seems rather premature to stop monitoring mild ARIA-E after just two follow-up MRI scans.

The Applicant stated that there is no need for MRI monitoring following resolution of the 2nd moderate or severe ARIA-E event. However, the argument that only 0.7% of aducanumab treated patients had a moderate or severe 3rd ARIA event could be related to study duration, and it could be argued that follow-up was too short to detect a 3rd moderate or severe ARIA event. It should be noted that after the first moderate or severe ARIA-E event, the majority of patients who had a 2nd ARIA event, had an event of moderate or severe severity.

The Applicant proposed that if treatment-emergent brain microhaemorrhages or localised superficial siderosis are noted on an MRI, patients should continue dosing once the microhaemorrhages or the localised superficial siderosis are radiographically stable on follow-up MRI. Even for patients with severe treatment-emergent brain microhaemorrhages or localised superficial siderosis noted on an MRI, treatment should be continued with caution after radiographic stabilization and clinical evaluation. It is noted that in the clinical trials patients with severe ARIA-H discontinued treatment permanently as per study protocol rules. Thus, the recommendation to continue treatment when the severe ARIA-H achieved radiological stabilization and following clinical evaluation is not supported by data. Also, this recommendation contradicts with the proposed contraindication: "Any pre-treatment localised superficial siderosis or 10 or more brain microhaemorrhages", assuming that "stabilization" means no change.

The MRI monitoring plan and when treatment should be stopped has been amended in accordance to the previous comments of the Rapporteurs', apart from recommendations concerning patients with ARIA-H superficial siderosis. In these patients, a distinction is made between mild or moderate (≤3 focal areas) and severe (≥3 focal areas) superficial siderosis. In line with the study data, patients with mild or moderate ARIA-H superficial sideroris, patients can continue dosing with caution only after radiographic stabilisation and clinical evaluation. In patients with severe ARIA-H superficial siderosis, dosing should be permanently discontinued.

Patients with cerebral small vessel disease such as lacunar infarct and diffuse white matter disease were excluded from the trials. Considering the potentially increased risk of ARIA in these patients, safety in this population would be of particular concern.

Data provided on laboratory findings is sufficient and did not raise concerns.

It is noted that a slightly higher proportion of patients treated with aducanumab reported SBP increase >160 mmHg (13.2%) compared to placebo (11.4%) in pool A1. At the same time, a slightly higher proportion of patients treated with aducanumab reported DBP increase >90 mmHg (18.9%) compared to placebo (17.9%) in pool A1. Similarly, a higher proportion of SBP increase >160 mmHg (13.8%) and DBP increase >90 mmHg (20.4%) was also reported in pool A2. The Applicant explained that SBP/DBP increase was more often observed in patients with elevated BP at baseline, but there was no difference between aducanumab and placebo treatments. The presented analysis does not indicate that treatment with aducanumab resulted in BP increase.

It is noted that relatively high numbers of patients had hypertension (placebo: 42.2%; aducanumab: 43.1%). The Applicant provided the list of all antihypertensive medications used with no clear discussion on which combinations of drugs were used and what changes during clinical trial occurred in the medication used. It appears that approximately a similar proportion of patients in the placebo group and aducanumab group were using anti-hypertensive medications (48,7% and 49.5%, respectively). The most common medications being amlodipine and lisinopril (6.5% and 6.8%, respectively).

While a rather similar proportion of patients treated with aducanumab (12.9%) and placebo (12.4%) reported weight decrease in the pool A1, it was a further higher proportion of patients treated with aducanumab reporting weight decrease (16.5%) in the pool A2, including long term open-label extension. It is agreed with the Applicant that most likely, the observed weight decrease in the long-term extension study is not an adverse event of aducanumab. However, it indirectly implies that the general condition of patients deteriorated at the same pace as the condition of patients described in the literature (not treated with aducanumab).

There were no markable differences in adverse event profiles between patients of different gender, races, regions, weights, clinical stages, or the use of Alzheimer's disease medication. Age-dependent differences seen are more likely related to the age itself than treatment. The small differences observed between patients with lower and higher body weight in the incidence of ARIA is most likely due to a lower total amount of aducanumab received. There are no data available in patients over the age of 85 years. Based on the adverse event profile, no major differences are expected in these patients compared to younger patients.

The incidence of anti-aducanumab antibodies is low, with an incidence of 0.5% in the total aducanumab group in Pool A1. There were no differences between the dose groups, and there was no relationship between immunogenicity and adverse events.

As aducanumab is a monoclonal antibody, the potential for drug-drug interactions is low. The use of antithrombotic medications has been identified as an aggravating factor for ARIA-H with other monoclonal antibodies directed against Aβ; therefore, non-aspirin anti-platelet agents and anticoagulants were disallowed as concomitant therapy. Concomitant treatment with aspirin and aspirin-containing medications at doses of ≤325 mg/day was allowed. The incidence of radiographically severe ARIA-H was somewhat higher in the patients taking concomitant aspirin or aspirin-containing medications as compared to those who did not use these medications: 6.1% vs 4.4%. Severe ARIA-H was observed in 5.8% of subjects receiving aducanumab and using aspirin and 4.2 of subjects receiving aducanumab without using aspirin. The relative risk of having severe ARIA-H in the aducanumab total group with concomitant aspirin use was 1.397 (95%CI 0.9679-2.0174).

The absolute risk is consistently higher in the group with concomitant aspirin use, irrespective of severity of ARIA-H and in moderate and severe or severe ARIA-H. However, it is acknowledged that the difference is small, and in all provided analyses, the confidence intervals overlap.

A similar proportion of patients with and without concomitant aspirin use with ARIA-H were symptomatic, and from those patients with symptoms, the distribution of severity of symptoms was similar.

Altogether it is unclear whether the risk of severe ARIA-H indeed is larger with concomitant aspirin use and what kind of advice would need to be mentioned in the SmPC in order to control the risk. However, there are no data on concomitant use of aducanumab and antiplatelet agents as treatment with aducanumab was discontinued if antiplatelet treatment was started during the study. Due to the higher risk of severe ARIA-H microhaemorrhage and ARIA-H macrohaemorrhage in these patients, the safety in this population is of particular concern.

2.5.9. Conclusions on the clinical safety

The safety profile of aducanumab is dominated by ARIAs. While the majority of these appear to be mild or moderate in MRI severity and apparently asymptomatic, some patients experience long-lasting, severe symptoms.

At the time of Opinion, there is insufficient information concerning the fatal case occurring in study 221AD304. The impact of this case on the overall safety profile of aducanumab is unclear.

Overall – and in line with the conclusions of the SAG – ARIAs are events of high relevance, whose knowledge (especially in its long term consequences) is insufficient. Furthermore, the feasibility of the monitoring required is questioned.

2.6. 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.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

Not applicable.

2.8. Product information

2.8.1. 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.*

2.9. New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that aducanumab could 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

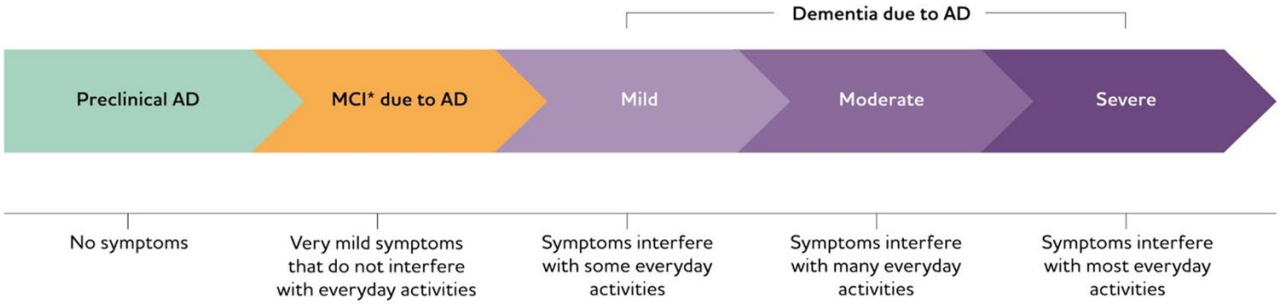
3.1.1. Disease or condition

AD is a progressive neurodegenerative disorder characterised by cognitive and functional decline. In general, initial impairment in memory and executive dysfunction is followed by a decline in other cognitive domains and behavioural and neuropsychiatric symptoms. A person's ability to perform usual daily life activities will decrease with the progression of the disease. In the severe stages of AD, patients die due to AD-associated comorbidity (e.g. pneumonia). Patients' life expectancy is variable and depends on various factors like age at onset and disease severity at the time of diagnosis.

AD is characterised biologically by the hallmark of two proteins: extra neuronal amyloid plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein. Abnormal protein deposition occurs over decades and leads to neurodegeneration and significant subsequent cognitive decline, ultimately leading to death.

Current understanding of AD describes a biological and clinical continuum (Figure 40), extending from preclinical phases of disease evidenced only by neuropathology without clinical symptoms, through the early symptomatic phases (e.g., Mild Cognitive Impairment (MCI) due to AD / prodromal AD), and ultimately AD.

Figure 40: Alzheimer's disease continuum



*MCI is the acronym for mild cognitive impairment
Figure derived from ALZHEIMER'S ASSOCIATION REPORT - 2020 Alzheimer's disease facts and figures

3.1.2. Available therapies and unmet medical need

No new medicines for AD have been introduced in the EU for over 15 years. Approved treatment options for patients with mild to moderately severe AD are the cholinesterase inhibitors (donepezil, rivastigmine,

and galantamine) and, for patients with moderate to severe AD, the N-methyl-D-aspartate antagonist; memantine. These agents provide symptomatic benefit with a limited duration of effect and no effect on the progression of the disease.

Hence, there is an unmet medical need for an effective and safe treatment in AD in an ageing European population in which the prevalence of AD increases.

3.1.3. Main clinical studies

The main studies of the clinical development program where studies 103, 301 and 302. Study 103 formed the proof of concept study informing the design of the two confirmative studies, i.e. Study 301 and 302 (Table 50).

Study 103 was a phase 1b, randomized, double-blind, placebo-controlled, staggered-randomisation, multiple-dose study assessing the safety, tolerability, PK and PD of aducanumab in patients with MCI due to AD or mild AD. The study had a long term extension but this was terminated early due to futility analysis of pivotal studies. Given its design and size, Study 103 it is considered exploratory and the benefits and risks are better characterised by the pivotal studies.

Study 301 and 302 were two identically phase III studies. Both had a randomised, multicentre placebo-controlled parallel-group study design with a 78-weeks placebo-controlled period. Subjects could enter a LTE wherein subjects on placebo were randomised a low (3 or 6 mg/kg) or high dose aducanumab (10 m/kg). During the LTE, the study remained blinded. The patients included in Studies 301 and 302 were patients with MCI due to AD or mild AD. A subset of patients was also included in a PET sub-study wherein a serial assessment of brain Aβ plaque levels by Aβ PET was conducted.

Table 50: Clinical development program of aducanumab

Study ID **No. of study centres/ locations** **Study period**	**Design** **Objective** **Duration**	**Dose at study initiation***	**Subjects by arm (ITT)** **Subjects in PET-substudy**	**Male/Female** **Age (median; range)** **APOE-ε status** **Diagnosis (Mild AD/MCI)**	**Primary and secondary endpoints**
221AD103 27 centres: US Oct 2012- Jul 2019	Phase 1b RD DB PC MD Safety & tolerability 52 weeks PC + LTE up to 5 years	Fixed: 1, 3, 6, or 10 mg/kg Titration: 1 to 10mg/kg All cohorts were placebo-controlled	196 total: 48 (placebo) 125 (fixed) 23 (titration) 167 total: 42 (placebo) 107 (fixed) 18 (titration)	98/98 73 (51-91) Carrier: 65% Noncarrier: 35% MCI: 43% Mild AD: 57%	Primary: Incidence of (S)AEs e.g. ARIA-E/ARIA-H Secondary: Δ from BL to Week 26 in 18F-florbetapir PET signal
221AD301 169 centres: US/EUR/CAN/ AUS/Asia Aug 2015- Aug 2019	Phase 3 RD DB PC PA Efficacy and safety 8 weeks prior to 1st dose + 78 weeks PC	Low dose after 8wks titration: 3 mg/kg for APOE-ε4 carriers 6 mg/kg for APOE-ε4 non-carriers High dose after 24wks titration: 6 mg/kg for APOE-ε4 carriers 10	1647 total: 545 (placebo) 547 (low dose) 555 (high dose) 585 total: 204 (placebo) 198 (low dose) 183 (high dose)	784/863 71 (50-85) Carrier: 69.5% Noncarrier: 30.3% MCI: 80.4% Mild AD: 19.6%	Primary: Δ from BL in CDR-SB at Week 78 Secondary: Δ from BL in MMSE at Week 78 Δ from BL in ADAS-COG13 at Week 78

	+ 18 weeks safety FU / LTE up to 5 years	mg/kg for APOE-ε4 non-carriers			Δ from BL in ADCS-ADL-MCI at Week 78
221AD302 181 centres: US/EUR/CAN/ Asia Sep 2015-Aug 2019	Phase 3 RD DB PC PA Efficacy and safety 8 weeks prior to 1st dose + 78 weeks PC + 18 weeks safety FU / LTE up to 5 years	Low dose after 8wks titration: 3 mg/kg for APOE-ε4 carriers 6 mg/kg for APOE-ε4 non-carriers High dose after 24wks titration: 6 mg/kg for APOE-ε4 carriers 10 mg/kg for APOE-ε4 non-carriers	1638 total: 548 (placebo) 543 (low dose) 547 (high dose) 488 total: 159 (placebo) 159 (low dose) 170 (high dose)	795/843 72 (50-85) Carrier: 66.8% Noncarrier: 32.8% MCI: 81.6% Mild AD: 18.4%	Primary: Δ from BL in CDR-SB at Week 78 Secondary: Δ from BL in MMSE at Week 78 Δ from BL in ADAS-COG13 at Week 78 Δ from BL in ADCS-ADL-MCI at Week 78

* During studies 301 and 302, the high dose for APOE-ε4 carriers was increased to 10mg/kg (protocol versions 4-6) based on analyses from cohort 4, study 103.
AD = Alzheimer's Disease, ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale, ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment, ApoE ε4 = apolipoprotein E ε4, ARIA-E = amyloid-related imaging abnormality-vasogenic edema, ARIA-H = amyloid-related imaging abnormality-microhemorrhage, macro-hemorrhage, or superficial siderosis, BL= baseline, CDR-SB = Clinical Dementia Rating-Sum of Boxes, DB = double-blind, FU = follow-up, ITT = intent-to-treat, LTE = long term extension, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, OLE = open label extension, PA = parallel group, PC = placebo-controlled, PET = positron emission tomography, PL = placebo, RD = randomised, Δ = change.

When the Phase III studies were running for more than 2.5 years, major amendments in the dosing regimen were made. At that time, about half of the patients in the Phase III studies were included. Initially, the aducanumab dose depended on ApoE ε4 status. In Study 103, ApoE ε4 carriers had a higher incidence of ARIA, which was dose-dependent with the highest incidence in the 10 mg/kg treated patients. Results of an additional cohort in this study showed that titration to 10 mg/kg reduced the incidence of ARIA-E as compared to started at once with the 10 mg/kg dose. For that reason, the dose for ApoE ε4 carriers in the Phase III studies was up-titrated from 6 mg/kg to 10 mg/kg.

A pre-defined futility analysis was conducted (26 December 2018) when 945 (57%) patients from Study 301 and 803 (49%) of patients from Study 302 completed the Week 78 visit. As the futility criteria were met, the DSMB recommended stopping the studies 103, 301 and 302. This was implemented on 21 March 2019. After the futility announcement on 21 March 2019, full evaluation of a larger dataset was conducted, containing blinded data collected from overrunning patients until the time the studies were stopped.

3.2. Favourable effects

In Study 301, none of the endpoints were met. There was no difference in change from baseline at Week 78 in CDR-SB between aducanumab high-dose (the dose applied for) versus placebo: 0.03 (2%, p=0.8330). No difference between placebo and aducanumab was observed after 78 weeks in any of the secondary endpoints (MMSE, ADAS-cog13, ADCS-ADL-MCI) or the tertiary endpoint (NPI-10).

In Study 302, the primary endpoint was met for high dose aducanumab. The difference in change from baseline at Week 78 in CDR-SB versus placebo was -0.39 (-22%, p=0.0120). For the secondary endpoints, the differences between the aducanumab high-dose group and placebo were for the change from baseline of the MMSE 0.6 (-18%, nominal p=0.0493), for the ADAS-Cog13 this was -1.40 (-27%,

nominal p=0.0097) and for the ADCS-ADL-MCI this was 1.7 (-40%, nominal p=0.0006). For the exploratory NPI-10 scale, this difference was -1.3 (-87%, nominal p=0.0215).

The estimates from the pooled analysis, reported in the effects table below, lie in between those from the two studies.

3.3. Uncertainties and limitations about favourable effects

Treatment effect

Both pivotal Studies were terminated for futility. The negative results (i.e. the below-threshold conditional power) on the futility dataset bears significance in the evaluation. In addition, the interruption of the studies limits the data available, especially to characterised long-term effect.

In contrast to Study 302, the identically designed Study 301 failed to show an effect also when overrunning patients were included. The Applicant has not demonstrated that the estimate from Study 302 (i.e. the existence of the effect) is more credible than the estimate from Study 301 (i.e. absence of an effect).

The Applicant states that two factors might have contributed to the different results of Study 301 and 302: i) an imbalance in the effect of a small number of participants with rapid progression and ii) differences in dosing due to Study 301 being more advanced when protocol versions allowing other doses were rolled out. None of the explanations are supported. The rapid progressors are few and excluding them has a minor impact. Furthermore, the observed fast progression is a post-randomisation event and excluding patients on that basis might bias the results. Regarding the assumed differences in dosing: both the mean cumulative doses (100.4 vs 103.3 mg/kg) and mean number of 10 mg/kg doses (7.1 vs 7.5) were almost identical in high dose groups in both studies. The post hoc analyses presented by the Applicant (and discussed above) have inconsistent results, and are in any case of exploratory nature, being data driven.

Furthermore, even the estimate of the effect from Study 302 does not cross the threshold for clinical relevance, as the difference with placebo is estimated at 0.39 (-22%, p=0.0120). This is below the value of 0.5 used at planning stage and supported in the literature as the minimal clinically relevant difference (Andrews et al, 2019[2]). This view is also supported by the SAG. The hypothesis that the effect is best expressed as a proportion of the decline prevented, and would be higher in longer studies is speculative and should be explored in dedicated studies. Given the concerns over the multiplicity control in place in the Study 302, further characterisation of the effect through the secondary endpoints is not fully inferentially valid.

Slightly less than half of the patients from the placebo-controlled phase rolled over into the long term extension (LTE). Furthermore, the LTE was terminated after 56 weeks, limiting the interpretation of the long term treatment effects of aducanumab.

A negligible association between change in cerebral amyloid-beta load and change in the primary endpoint was demonstrated in the phase III studies. This further questions the relevance of the mechanism of action.

[2] Scott Andrews et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials (2019). Alzheimer's & Dementia: Translational Research & Clinical Interventions 5; 354-363.

3.4. Unfavourable effects

The adverse event profile of aducanumab is dominated by central nervous system adverse events, specifically ARIAs and symptoms associated with these. In the pivotal trials, ARIA-E occurred in 2.7% of patients in the placebo group compared to 35.2% in the 10 kg/mg aducanumab group. ARIA-H incidence were also higher in the 10 kg/mg aducanumab group as compared to the placebo group (28.3% vs 6.5%, respectively).

A total of 31 deaths were reported in the aducanumab clinical development programme, while participants were enrolled in clinical studies (placebo: 6; aducanumab: 25). From these, the cause of death due to one cerebral haemorrhage was considered related to aducanumab by the investigator. An additional death was reported after the data cut-off, which occurred in study 221AD304. Insufficient information on the case is available at the time of opinion.

The majority of ARIAs were asymptomatic (78.1% in the total aducanumab group) and considered mild (38.5%) or moderate (43.0%) in MRI severity. In terms of symptom severity, most patients had mild symptoms (63.6%). 16.4% of aducanumab-treated patients who had an ARIA event discontinued treatment.

In those patients with symptomatic ARIA, the most common ARIA-related adverse events in the aducanumab-treated patients were headache (50.6%), confusional state (15.3%), dizziness (10.2%), nausea (6.8%) and fatigue (5.1%). Altogether, 6 participants had seizure events concurrent with ARIA-E events in the pooled studies of aducanumab.

According to the imaging-based scoring, Serious ARIA-E occurred in 1 patient in the placebo group (<0.1%) and in 22 patients in the aducanumab group (1.0%). In terms of ARIA-H, there was 1 patient in the placebo group with serious ARIA-H microhaemorrhage event (<0.1%) as compared to 8 in the aducanumab group (0.4%). Serious ARIA-H macrohaemorrhage event occurred in 1 patient in the aducanumab group (<0.1%) and serious ARIA-H superficial siderosis event in 6 patients in the aducanumab group (0.3%) as compared to none in the placebo group. In all cases but one, the events were resolved. In the unresolved case, the patient died before ARIA-E was resolved. Most serious ARIAs occurred in patients who are ApoE ε4 carriers. From those patients in the aducanumab total group in Pool A1 who had ARIA-E and had at least one dose and one MRI after the first ARIA-E resolution, 36.8% experienced a second ARIA-E event. The characteristics of the second event i.e. MRI severity and symptomatic status were in general similar to those of the first. The majority of events (97.9% in the total aducanumab group) resolved.

3.5. Uncertainties and limitations about unfavourable effects

ARIAs are relatively new imaging phenomena, with variable (but sometimes severe) clinical manifestations. The long-term clinical consequences of ARIA (especially in case of long-term treatment) have not been sufficiently characterised. The reduced size of the LTEs of the phase 3 studies is one of the sources of such uncertainty.

During clinical studies, ARIA; the most common ADR of aducanumab, was monitored by MRI, and in the case of ARIA detection, MRI monitoring was performed more often. The feasibility of this intensive monitoring is questioned, as also confirmed by the SAG.

One death in the clinical studies due to cerebral haemorrhage was considered related to aducanumab by the investigator, which was later challenged via re-review of MRIs. It cannot be concluded whether aducanumab possibly aggravated the existing neurovascular pathology in a patient dying due to cerebral haemorrhage, due to several other confounding factors.

Detailed information on the fatal case occurring in study 221AD304 is not available at time of the opinion, and the causality assessment is subject to uncertainty.

3.6. Effects Table

Table 51: Effects Table for Aducanumab

Effect	Short description	Unit	Placebo	High Dose Aducanumab	Uncertainties / Strength of evidence	References
Favourable Effects						
CDR-sb	Composite cognitive and functional scale	-	1.64	1.46 (difference -0.17, p=0.1)	Only significant in Study 302	Pooled analysis of Studies 301 and 302
ADAS-Cog13	Cognitive scale	-	5.15	4.17 (difference -0.98, p=0.01)	Only nominally significant (no adequate T1E control) in Study 302	Pooled analysis of Studies 301 and 302
ADCS-ADL-MCI	Functional scale	-	-4	-2.8 (difference 1.2,p=0.0004)	Only nominally significant (no adequate T1E control) in Study 302	Pooled analysis of Studies 301 and 302
Unfavourable Effects						
ARIA-E	Different imaging and clinical severities	%	2.7%	35%	Imaging phenomena with heterogeneous clinical presentation and unclear long-term clinical consequences. Incidence with intensive MRI monitoring of uncertain feasibility in practice.	Safety Pool A1
ARIA-H	Different imaging and clinical severities	%	6.5%	19.1%		
Siderosis	Superficial siderosis of the CNS	%	2.2%	14.6%		

ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale, ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living –Δ = difference
(1) CSR Study 301
(2) CSR Study 302
(3) Pooled data of placebo-controlled phases of studies 301 and 302.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects and the associated uncertainties

The two pivotal trials for Aducanumab were interrupted for futility. Even with overrunning patients, one of the two trials is negative. Hence, no effect can be considered demonstrated.

Even if the point estimates for efficacy from the final analysis of Study 302 or from the pooled analysis were to be believed (which is not the case), the clinical relevance is questioned, as also confirmed by the SAG. Even the estimate from Study 302 is smaller than the effect size considered worthwhile at the

planning stage and used in the sample size calculations, i.e. 0.5 points. This threshold is also considered the minimal clinically relevant difference in the literature. A questionable clinically relevant difference of the observed effect estimates also applies to the secondary clinical endpoints.

The hypothesis that the effect is best expressed as a proportion of the decline prevented, and would be greater with a longer trial, is just speculative. Of note, in the scientific advice by the CHMP, a duration of 78 weeks was also questioned because of the risk of not being sufficient to fully characterise the effect, due to the slow decline in this population.

In the phase III PET sub-studies, a reduction in cerebral amyloid load was observed in patients who received aducanumab as compared to placebo. However, this can only be considered as a confirmation of the pharmacological activity of Aducanumab. The lack of individual-level correlation between such reduction and clinical outcome further lowers the importance of this outcome.

Importance of unfavourable effects and the associated uncertainties

Aducanumab is associated with central nervous system adverse events, particularly ARIAs and symptoms related to these, such as headache. Even though most patients experience only one ARIA, which is asymptomatic and mild in MRI severity, some patients suffer a serious ARIA with severe symptoms which have not resolved despite treatment discontinuation. Furthermore, even if symptoms are mild or moderate, it may take weeks before they resolve, which is considered problematic in patients who already suffer from CNS symptoms due to AD.

Long-term effect of ARIAs, especially in presence of long-term treatment, have not been sufficiently characterised. The ARIA MRI monitoring programme proposed might not be feasible, even in specialised centres, as confirmed by the SAG.

A recently reported fatal case possibly related to ARIA-E and aducanumab is pending assessment and its impact on the benefit-risk profile of aducanumab is currently unclear.

3.7.2. Balance of benefits and risks

To conclude, aducanumab's efficacy in mild cognitive impairment due to AD and mild AD has not been demonstrated, whereas the treatment poses patients at the risk of ARIAs where the clinical relevance of this is unknown on the long term.

3.7.3. Additional considerations on the benefit-risk balance

On October 29 2021, a SAG Neurology meeting was convened upon request of the CHMP. Next to the SAG members, additional experts were present. The following issues were discussed:

1. Does the expert group consider that the data presented robustly demonstrate efficacy of aducanumab on clinical endpoints in the target population?

The experts unanimously consider that the contradictory evidence from these two, equally powered, phase 3 studies does not allow to consider that a robust demonstration of efficacy was achieved.

The experts expressed the view that the premature termination of the studies further lowers the credibility of the positive finding in the high dose group only in one of the trials.

The plurality of post-hoc analyses has been also commented. Some of the analyses have been particularly criticised by the experts – including those that exclude patients from the analysis based on observed post-baseline characteristics such as disease progression. A major concern was also related to the absence of statistical protection against multiple comparisons. Overall, the post-hoc analyses are

considered nothing more than hypothesis-generating, and the main evidence comes from the pre-specified analyses on the ITT populations.

Results from previous randomised controlled trials of other amyloid-targeting molecules to some extent corroborate this view, but are not a decisive argument. Nonetheless, the experts do not unanimously discard the possibility that – in the future – the amyloid hypothesis could translate in efficacious treatments, maybe on a more restricted population (earlier stages) and/or in association with drugs targeting other pathological mechanisms. It should be noted that also the experts who believe the amyloid hypothesis could in the future translate in efficacious treatments believe the results presented do not demonstrate efficacy.

The suitability of CRD-SB as the preferred scale for the clinical endpoint was also challenged as it is not considered to be fully validated for MCI but rather better suited to designate the severity of dementia due to AD.

a. If the answer is positive, does the expert group consider that the estimated efficacy from the pooled analysis is clinically relevant?

Despite the negative answer to the first question, the group discussed this topic and concluded that the estimates of the effect, both from the pooled analysis and from the positive study only, are considered very modest with uncertain clinical relevance, especially when expressed in absolute and not relative terms. The experts commented that the modest effect on the outcomes used should be considered in light of the adverse events that are frequent, potentially severe and difficult to manage in the clinical practice (see below) and, therefore, maintaining an unfavourable benefit/risk ratio.

b. If the answer is negative, what does the expert group consider needed to robustly demonstrate clinical efficacy of aducanumab in the target population?

A new phase 3 trial on clinical endpoints, planned and conducted with adequate power to detect clinically relevant effects on both cognitive and functional endpoints (considered as dual primary clinical outcomes), and with an adequate dosing schedule could demonstrate clinical efficacy. Given the hypothesis of an effect growing over time, a longer duration might be considered. A duration of 3 years was considered as the minimum to maximise the chance to observe a clinically relevant effect on clinical outcomes in the target population, specially if restricted to early stages (see below).

The possibility of recruiting an earlier-stage and more homogeneous population has been suggested by some of the experts. However, the population should be identifiable in practice to ensure sufficient external validity of the results. It was also noted that a population in earlier stages of the disease would require a much longer trial that may be more difficult to conduct.

Some of the experts mentioned that – given the effect size and the uncertainties – replicating Study 302 in both methods and results in one study would not be sufficient. Some of the experts doubted whether in case of a positive result of a new, well-conducted RCT as described above, study 302 could serve as supporting positive study, considering the answer to question 1.

Some of the experts proposed a sub-study characterising extent and variability of BBB penetration could also be considered.

Some of the experts made the point that another phase 3 trial would be futile and therefore unethical, but the majority of experts considered that a phase 3 trial would have equipoise and therefore be justified if adequately planned.

i. Is demonstrating a surrogate threshold effect of amyloid reduction sufficient?

The group unanimously expressed the view that amyloid is not a validated surrogate biomarker and cannot be used as a surrogate of efficacy in this setting. The relation between amyloid load in the brain and cognitive functioning is uncertain, particularly in higher age groups.

An extensive body of literature, including numerous randomised controlled trials, supports the notion that removal of amyloid from the brain does not automatically translate into a measurable effect on cognition.

2. The expert group is asked to comment on the clinical relevance of ARIA-Es and ARIA-Hs and the manageability of these imaging abnormalities in clinical practice.

SAG experts unanimously considered that ARIA-E and ARIA-H are of high clinical relevance, because of their high frequency and the potentiality of life-threatening events.

The experts commented that the knowledge of these events is still incomplete. Even though it has been acknowledged that severe clinical consequences of ARIA-E seem quite rare, it was reiterated that not enough data are available on the long-term consequences of ARIA-E. The feasibility of the MRI management that appears necessary in clinical practice has been questioned, even in highly specialised centres. The experts considered also that the burden on patients should be taken into account.

3.8. Conclusions

The overall benefit/risk balance of Aduhelm is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Aduhelm in the proposed indication, MCI and mild dementia due to AD, the CHMP considers by consensus that safety and efficacy of the above-mentioned medicinal product are 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:

- Efficacy in MCI and mild dementia due to AD has not been demonstrated:
  - The application includes two pivotal studies, both prematurely terminated for futility. The post-hoc analyses of these studies presented lack, by their nature, of confirmatory value and have results that are, in any case, not in line with the hypothesis formulated by the Applicant. Moreover, the two studies have inconsistent results at the final analysis;
  - Furthermore, the efficacy estimated from the study for which the final analysis is positive is not considered clinically relevant, because of the size of the estimated efficacy which is below the minimal clinically important difference;
- Safety has not been adequately demonstrated:
  - Aducanumab treatment can cause serious amyloid-related imaging abnormalities (ARIA) with risk of clinically relevant harmful effects;

- Furthermore, both the feasibility and the effectiveness of the risk mitigation measures proposed have not been sufficiently demonstrated.

It is the opinion of the CHMP that considering the lack of proof of efficacy of aducanumab, and the potential serious safety risks, the benefit-risk balance in the claimed indication is negative.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety and efficacy of the above-mentioned medicinal product are not properly or sufficiently demonstrated.

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 previously outlined in the list of outstanding issues cannot be agreed at this stage.