25 April 2024
EMA/89198/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal variation assessment report

Amyvid

International non-proprietary name: florbetapir (18F)

Procedure No. EMEA/H/C/002422/II/0046

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	28 Oct 2023	28 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	21 Dec 2023	22 Dec 2023	☐
☐	PRAC Rapporteur Assessment Report	03 Jan 2024	n/a	☐
☐	PRAC members comments	04 Jan 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	05 Jan 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Jan 2024	11 Jan 2024	☐
☐	CHMP members comments	15 Jan 2024	15 Jan 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Jan 2024	18 Jan 2024	☐
☐	Request for Supplementary Information	25 Jan 2024	25 Jan 2024	☐
☐	Submission deadline	23 Feb 2024	23 Feb 2024	☐
☐	Re-start of procedure	26 Feb 2024	26 Feb 2024	☐
☐	CHMP Rapporteur Assessment Report	02 Apr 2024	15 Apr 2024	☐
☐	CHMP members comments	15 Apr 2024	17 Apr 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Apr 2024	19 Apr 2024	☐
☒	2nd Request for Supplementary Information	25 Apr 2024	25 Apr 2024	☐
☐	Submission deadline	16 Aug 2024		☐
☐	Re-start of procedure	19 Aug 2024		☐
☐	CHMP Rapporteur Assessment Report	23 Sep 2024		☐
☐	CHMP members comments	07 Oct 2024		☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 Oct 2024		☐
☐	Opinion	17 Oct 2024		☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur:	Martina Weise

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List of abbreviations

Term	Definition
AD	Alzheimer's disease
ADR	adverse drug reaction
CE	Conformité Européene
CSF	cerebrospinal fluid
CHMP	Committee for Medicinal Products for Human Use
GVP	Good Pharmacovigilance Practices
HTA	Health Technology Assessment
MAA	Marketing Authorisation Application
PBRER	periodic benefit-risk evaluation report
PET	positron emission tomography
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
RMP	risk management plan
SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 10 October 2023 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include monitoring response to therapy for AMYVID, based on supporting literature. As a consequence, sections 4.1 and 4.4 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.8 of the SmPC to reflect the current clinical trial exposures to align it with the updated RMP.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include monitoring response to therapy for AMYVID, based on supporting literature. As a consequence, sections 4.1 and 4.4 of the SmPC are updated. The Package Leaflet is updated in accordance.

☐ is recommended for approval.

☐ is not recommended for approval.

☒ is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)

☒ 60 days (36 days to assess)

Further, Version 5.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.8 of the SmPC to reflect the current clinical trial exposures to align it with the updated RMP. These parts of the variation

☐ are recommended for approval.

Grounds for refusal

N/A

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

3. Recommendations following re-examination

N/A.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'

5. Scientific discussion

5.1. Introduction

The current variation procedure includes 3 components to be approved: 1. New indication: “Imaging of β amyloid neuritic plaque density in the brains of adult patients receiving amyloid-targeting therapy”; 2. Adjustment of patient exposure in the section 4.8 of the SmPC (presented in section 5.5) and 3. An adapted RMP (presented in section 6).

These topics are being discussed and assessed individually below.

Of note, on 13 July 2023, Eli Lilly and Company (Lilly) submitted a Type II variation (procedure number: EMEA/H/C/002422/II/0044) to remove the limitation statement on non-established efficacy regarding monitoring response to therapy from the Amyvid summary of product characteristics (SmPC), section 4.4 Warnings and Precautions. A preliminary assessment report was circulated to Lilly on 6 September 2023 including requests for supplementary information.

During the Committee for Medicinal Products for Human Use (CHMP) plenary meeting of 11 to 14 September 2023, the Amyvid II-44 procedure was discussed, and it was concluded that the variation procedure chosen was not appropriate. CHMP recommended the Amyvid II-44 procedure to be withdrawn and resubmitted as extension of indication (scope classification C.I.6) to add monitoring response to therapy as a new indication to the Amyvid SmPC.

Following CHMP recommendation, Lilly withdrew the Type II variation EMEA/H/C/002422/II/0044 on 29 September 2023 and submitting the current application to add monitoring response to therapy as a new indication for florbetapir. Lilly acknowledged the requests for supplementary information 1 to 9 (Major Objection and Other Concerns, Clinical Aspects) received under the scope of the II-44 procedure, but did no consider these at the time of submission. Only responses to the requests for supplementary information received in II-44 procedure related to the SmPC and RMP in appendices 2 and 3 of the Clinical Overview addendum were submitted.

Notes:

The company did not provide proper addendum to the clinical overview to present and discuss data supporting the new indication at the time of submission, limiting the content only to the responses to SmPC and RMP as mentioned above. Therefore, the part of the assessment in this report includes the information submitted for the variation procedure EMEA/H/C/002422/II/0044 and the respective somewhat adapted preliminary assessment.

The Applicant has now provided responses to the FIRST RSI.

Throughout the document wherever the substances used as tracers (e.g., flortaucipir, florbetapir) are used 18F-labelled tracer is meant, unless specified otherwise.

5.1.1. Problem statement/About the product

Florbetapir (^{18}F) (Amyvid®) was approved on 14 January 2013 in the EU as a diagnostic radiopharmaceutical for PET imaging of β-amyloid neuritic plaques in the brain of patients with cognitive impairment being evaluated for suspected AD and other causes of cognitive impairment. Currently valid indication is

"This medicinal product is for diagnostic use only.

Amyvid is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. Amyvid should be used in conjunction with a clinical evaluation.

A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD. For the limitations in the interpretation of a positive scan, see sections 4.4 and 5.1."

At the time of florbetapir's initial approval, there were no longitudinal follow-up PET scan data with effective anti-amyloid therapies to show that PET scans could be used to reliably monitor pharmacological response to therapy. The Applicant is of the opinion that there is a large amount of literature and experience supporting the efficacy of florbetapir (and other amyloid-imaging agents) for monitoring of treatment effects on brain amyloid of the patients with AD and that these data are sufficient to grant new indication.

5.1.2. The development programme/compliance with CHMP guidance/scientific advice

Only published literature has been presented. No scientific advice was sought. The presented addendum to clinical overview is not adequate as it does not discuss relevant aspects required by the relevant guidance documents on diagnostic agents (CPMP/EWP/1119/98/Rev.1 and EMEA/CHMP/EWP/321180/2008).

5.1.3. General comments on compliance with GCP

Not applicable, since data from own studies not presented.

5.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

5.2.1. Ecotoxicity/environmental risk assessment

A new ERA dated on the 8th of October 2023 was provided. The ERA cites two logK_{ow} studies which were already provided and assessed during the initial application. One for Florbetapir (^{18}F) ('shake-flask'; logK_{logKow} at pH 7.4 = 1.74) and one for Florbetapir (^{19}F) ('potentiometric'; logK_{ow} in 'water' = 3.4). A PBT screening is still not deemed necessary.

The PEC for surface water (PEC_{sw}) does not change by the introduction of the new indication. The PEC_{sw} was calculated with default values to be below the threshold value for a Phase II assessment, which was already an overestimation since the product is only be used for diagnosing purposes and not on a daily basis. Since 'monitoring' is the new indication and the PEC_{sw} was calculated with default values this new indication will not lead to a surpass of the threshold value for a Phase II assessment.

The ERA can still stop in Phase I.

5.2.2. Discussion on non-clinical aspects

The ERA has shown that an in-depth ERA is not considered necessary, the ERA can stop in Phase I

5.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of florbetapir.

Considering the above data, florbetapir is not expected to pose a risk to the environment.

5.3. Clinical aspects

GCP

Not applicable, since own data have not been presented.

- Tabular overview of clinical studies not provided

PK, PD, PK/PD have not been discussed.

5.3.1. Clinical pharmacology

Drug-drug interactions/competitive binding at target location

Potential drug-drug interactions were explored between florbetapir using an in vitro tissue binding assay and an in vitro film autoradiography. The drugs tested included the following approved drugs:

- non-steroidal anti-inflammatory drugs ibuprofen, naproxen, and celecoxib
- acetylcholinesterase inhibitors tacrine, physostigmine, galantamine, and donepezil
- cholesterol-lowering drug simvastatin
- anti-diabetic drug troglitazone
- anti-psychotic drug haloperidol
- anxiolytic diazepam, and
- anti-depressants citalopram, fluoxetine, paroxetine, and nisoxetine.

In addition, an anti-Aβ-antibody (Crenezumab; Roche) and 4 γ-secretase inhibitors (L-685458, S1288, Compound W, and DAPT) were tested. The results were previously submitted in the Amyvid marketing authorisation application in Technical Report TR-AV-45-081 (Module 4.2.1.4) and demonstrated no risk for drug-drug interactions at the florbetapir-binding site.

Similar competition-binding studies were also later performed with donanemab and lecanemab, and similarly weak competitive binding was observed. Results are provided for the filtration-binding studies (NS48 Report; Module 4.2.1.4). Donanemab inhibited ^{18}F-florbetapir binding at the top concentration in both studies (1 µM); an IC50 for donanemab is estimated to be ≥1 µM. Lecanemab showed weak or no inhibition in the 2 studies; an IC50 for lecanemab could not be extrapolated.

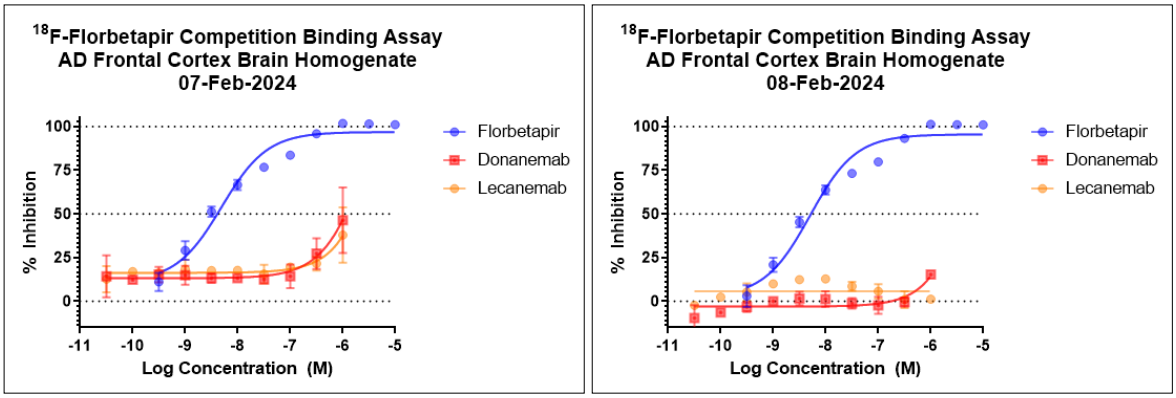


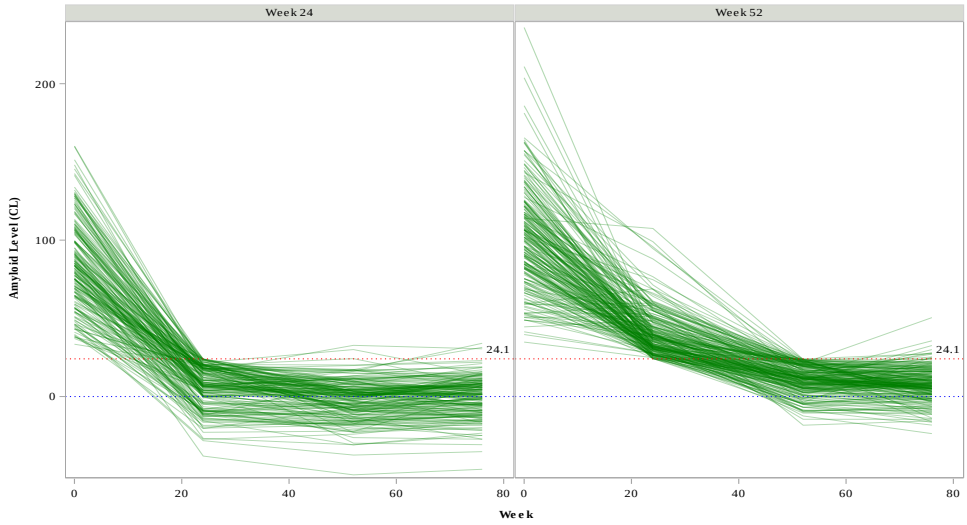
Figure 1 Inhibition curves of donanemab and lecanemab.

Donanemab CSF levels from patients in the Phase 1 AACD study, evaluated post 10 mpk dose, were 1.39 ± 0.62 nM (208 ± 93 ng/mL). In contrast, donanemab had no effect on ^{18}F-florbetapir binding at concentrations ≤320 nM (greater than 200x CSF levels). Similarly, published CSF levels for lecanemab (Logovinsky et al. 2016), post 10 mpk dose, were 1.75 ± 0.71 nM (263 ± 106 ng/mL), which is greater than 180-fold less than 320 nM, the lowest lecanemab concentration that affected ^{18}F-florbetapir binding. Based on the clinical CSF levels of these amyloid-targeted treatments, neither donanemab nor lecanemab treatment would be expected to interfere with ^{18}F-florbetapir binding to amyloid.

Possible factors influencing florbetapir uptake/binding during treatment with anti-amyloid antibodies/amyloid-targeting treatments (e.g., via a competitive binding at the target location, or due to ARIA/other AEs, or immunological /other pathophysiological processes which may be affecting the uptake/binding of florbetapir at the target location, or changes in the structure of the amyloid, that may affect Florbetapir binding) should be discussed based on the clinical and non-clinical evidence

Data from the donanemab programme indicate that re-accumulation rates for patients who stopped donanemab treatment were consistent with the rates of accumulation in natural history studies (Shcherbinin et al. 2023). Also, refer to Figure APP 5.2, where any individual re-accumulation in patients achieving amyloid clearance at 24 or 52 weeks (many of whom met stopping criteria and ceased treatment at that time) is significantly below the baseline amyloid level over the following 6 to 12 months.

Figure 2. APP 5.2. Spaghetti plot of amyloid level (CL) over time by amyloid cleared visit Double-blinded treatment period; Evaluable efficacy set (EES); Study I5T-MC-ACCI (primary outcome database lock).

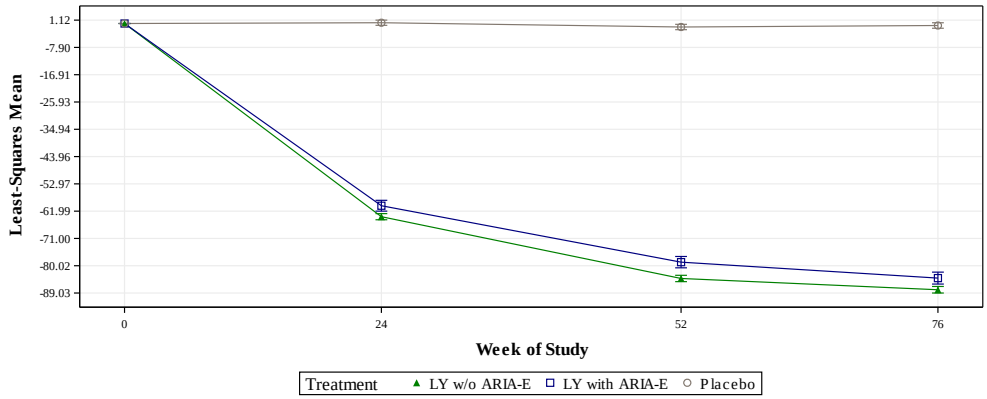


Additionally, further non-clinical data supporting that changes in florbetapir uptake after treatment with ATTs are unlikely to be a consequence of competitive binding is provided in response to question 3.

Further, in case possible pathophysiological processes, such as perfusion changes or ARIA or other AE, impacted amyloid PET signal, it would be expected that similar effects would be observed with tau-PET signal as well. Data from the donanemab Study AACI clearly demonstrate that, at difference with amyloid PET, tau PET signal is not reduced in patients treated with ATTs, with rather some marginal evidence for slowing of tau accumulation in subsets of patients (Sims at al. 2023).

Additionally, within the donanemab programme, sensitivity analyses based on ARIA indicated that there was no material difference between the level of amyloid clearance observed, regardless of whether patients experiencing ARIA over the course of the trial were included or excluded from the analysis.

Figure 3. Plot of Florbetapir Centiloid Longitudinal Avid Analysis - Change from Baseline by Treatment and ARIA-E Status; LS-Mean Estimates from MMRM Model; Evaluable Efficacy Set (EES) Study I5T-MC-AACI (Primary Outcome Database Lock) All EES Participants



5.3.2. Conclusions on clinical pharmacology

Data related to PK, PD, PK/PD have not been presented or discussed. With the responses to the first RSI some data on drug-drug interactions, competitive binding vs AATs, etc. have been submitted, which do not reveal specific confounders. (see the detailed assessment in the discussion of efficacy).

5.4. Clinical efficacy

To support the proposed change in the SmPC the Applicant has submitted 13 publications describing the studies evaluating anti-amyloid therapy where amyloid PET was applied for monitoring of the treatment effects and one review article:

- solanezumab (Fleisher et al. 2017; Honig et al. 2018; Salloway et al. 2021)
- bapinezumab (Brody et al. 2016)
- donanemab (Lowe et al. 2021; Mintun et al. 2021; Shcherbinin et al. 2022; Sims et al., 2023)
- crenezumab (Salloway et al. 2018)
- lecanemab (Swanson et al. 2021; van Dyck et al. 2023)
- gantenerumab (Klein et al. 2019; Bateman et al. 2022), and
- aducanumab (Budd Haeberlein et al. 2022).

Additionally, the Applicant states that as of June 2023, there were 49 trials registered on clinicaltrials.gov that list amyloid PET tracers as an outcome measure for monitoring pharmacological response to intervention. Of these 49 trials, 31 trials had reached their completion date. Results have not been provided.

Data described in the published studies have not been discussed in detail, but the following has been summarised in the addendum to the Module 2.5:

"… research over the last decade has shown that amyloid PET is indeed responsive to amyloid-targeted therapy. While no data exists to show that amyloid lowering predicts clinical response to therapy on an individual patient level, evidence suggests that amyloid-targeting therapies must reduce brain amyloid to be clinically effective. Studies with statistically positive results had early and marked reduction in amyloid, whereas failed studies had slow or incomplete amyloid lowering. Agents that target deposited plaque in the brain show more rapid reduction of amyloid PET signal (for example, donanemab [Mintun et al. 2021], aducanumab [Budd Haeberlein et al. 2022], and lecanemab [van Dyck et al. 2023]), whereas agents targeting circulating amyloid species appear to lower brain amyloid PET signal slowly, if at all (for example, solanezumab [Honig et al. 2018], β-site amyloid precursor protein–cleaving enzyme 1 inhibitors [Egan et al. 2018; Wessels et al. 2020]). Further, in a recent disclosure by Barkhof et al. (2023) it was reported that the level of clinical benefit achieved by participants in the Phase 3 gantenerumab trials was proportional to the amount of clearance on amyloid PET. Based on recent compelling Phase 2 (Mintun et al. 2021) and Phase 3 data from amyloid-targeting plaque antibodies donanemab (pre-publication manuscript; data on file; MAA submission expected in July 2023) and lecanemab (Van Dyck et al. 2023; MAA currently under assessment), there is stronger evidence that disease-modifying therapies that reverse the neuropathology of AD also slow the cognitive and functional decline associated with progression of brain pathology."

5.4.1. Published evidence of efficacy – more relevant studies

Sims et al., 2023. Donanemab in Early Symptomatic Alzheimer Disease The TRAILBLAZER-ALZ 2 Randomized Clinical Trial (Funded by Eli Lilly; TRAILBLAZER-ALZ 2 Clinical- Trials.gov number, NCT04437511.)

TRAILBLAZER-ALZ 2 was a 76-week, phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled trial with participants screened at 277 sites in 8 countries.

Eligible participants had screening Mini-Mental State Examination (MMSE) scores of 20 to 28, amyloid pathology (≥37 Centiloids) assessed with florbetapir or florbetaben PET, and presence of tau pathology assessed by flortaucipir PET imaging with central image evaluation. Tau PET scans were categorized as low/medium or high tau by visual and quantitative reads.

Eligible participants were randomly assigned in a 1:1 ratio with stratification by baseline tau categorization and enrolling sites; the randomization block size was 4. Randomized participants received either donanemab (700 mg for the first 3 doses and 1400 mg thereafter) or placebo, administered intravenously every 4 weeks for up to 72 weeks. If amyloid plaque level (assessed at 24 weeks and 52 weeks) was less than 11 Centiloids on any single PET scan or less than 25 but greater than or equal to 11 Centiloids on 2 consecutive PET scans donanemab was switched to placebo in a blinded procedure.

The primary outcome was change in the iADRS score from baseline to 76 weeks in either the low/medium tau population or combined (low/medium and high tau) population (iADRS; range, 0 to 144, with lower scores indicating greater cognitive and functional impairment).

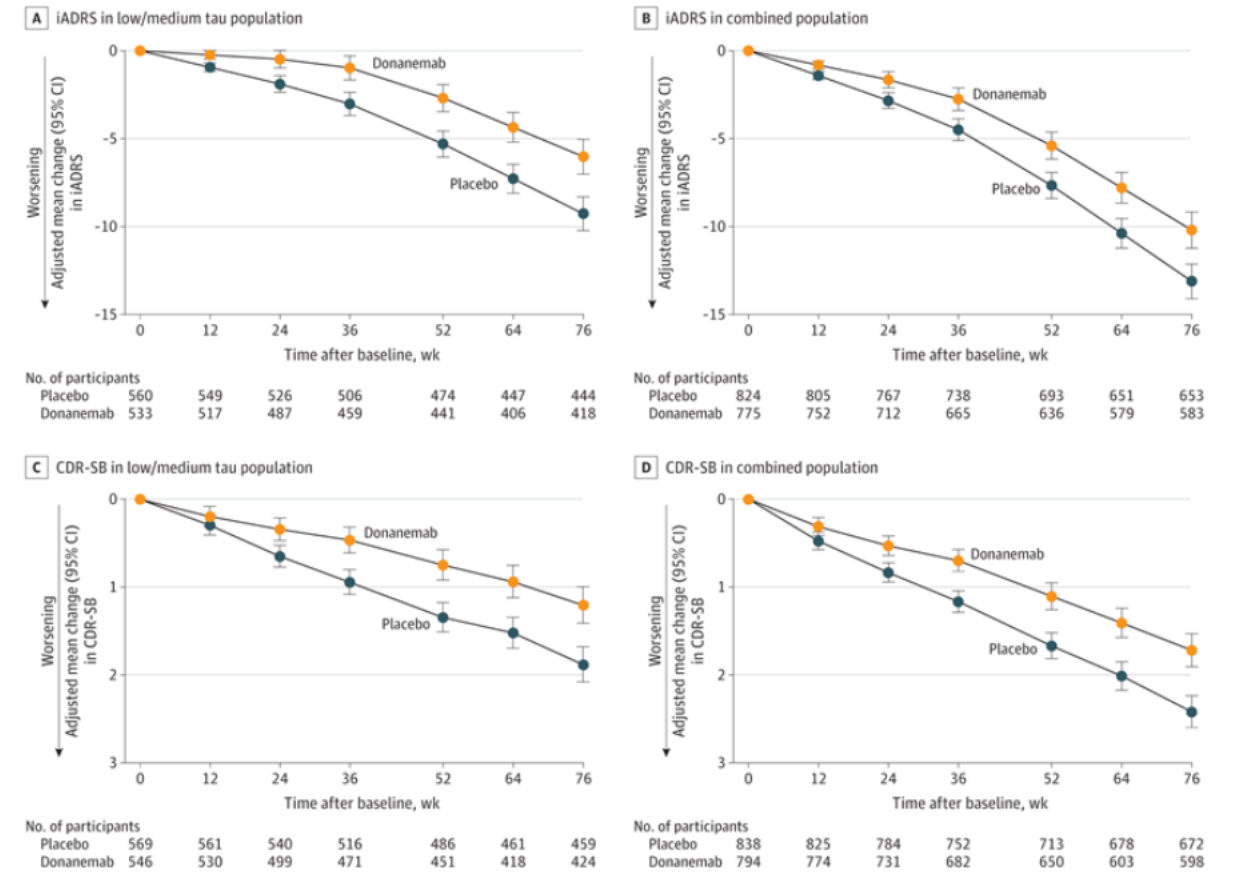
Prespecified secondary outcomes included changes from baseline to 76 weeks by sum of boxes of the Clinical Dementia Rating Scale (CDR-SB), the ADAS-Cog_{13}, the ADCS-iADL, and MMSE in the low/medium tau or combined population. Amyloid plaque reduction at 76 weeks, percentage of participants reaching amyloid clearance (<24.1 Centiloids measured by amyloid PET) at 24 weeks and 76 weeks, tau PET[1] (frontal cortical regions) change, volumetric MRI (vMRI; whole brain, hippocampus, and ventricles) change, and adverse events were additional secondary outcomes.

RESULTS

Of 8240 participants screened, 1736 were enrolled (mean age, 73.0 years; 996 [57.4%] women) and 76% completed the trial: 860 were assigned to receive donanemab and 876 were assigned to receive placebo. As expected, the combined population had higher tau biomarkers at baseline due to the inclusion of participants with high tau pathology and showed greater impairment across baseline clinical assessments.

In the low/medium tau population, LSM change from baseline in the iADRS score at 76 weeks was −6.02 (95% CI, −7.01 to −5.03) in the donanemab group and −9.27 (95% CI, −10.23 to −8.31) in the placebo group (difference, 3.25 [95% CI, 1.88-4.62]; $P < .001$), representing a 35.1% (95% CI, 19.90%-50.23%) slowing of disease progression. In the combined population, LSM change from baseline in the iADRS score at 76 weeks was −10.19 (95% CI, −11.22 to −9.16) in the donanemab group and −13.11 (95% CI, −14.10 to −12.13) in the placebo group (difference, 2.92 [95% CI, 1.51-4.33]; $P < .001$), representing a 22.3% (95% CI, 11.38%-33.15%) slowing of disease progression.

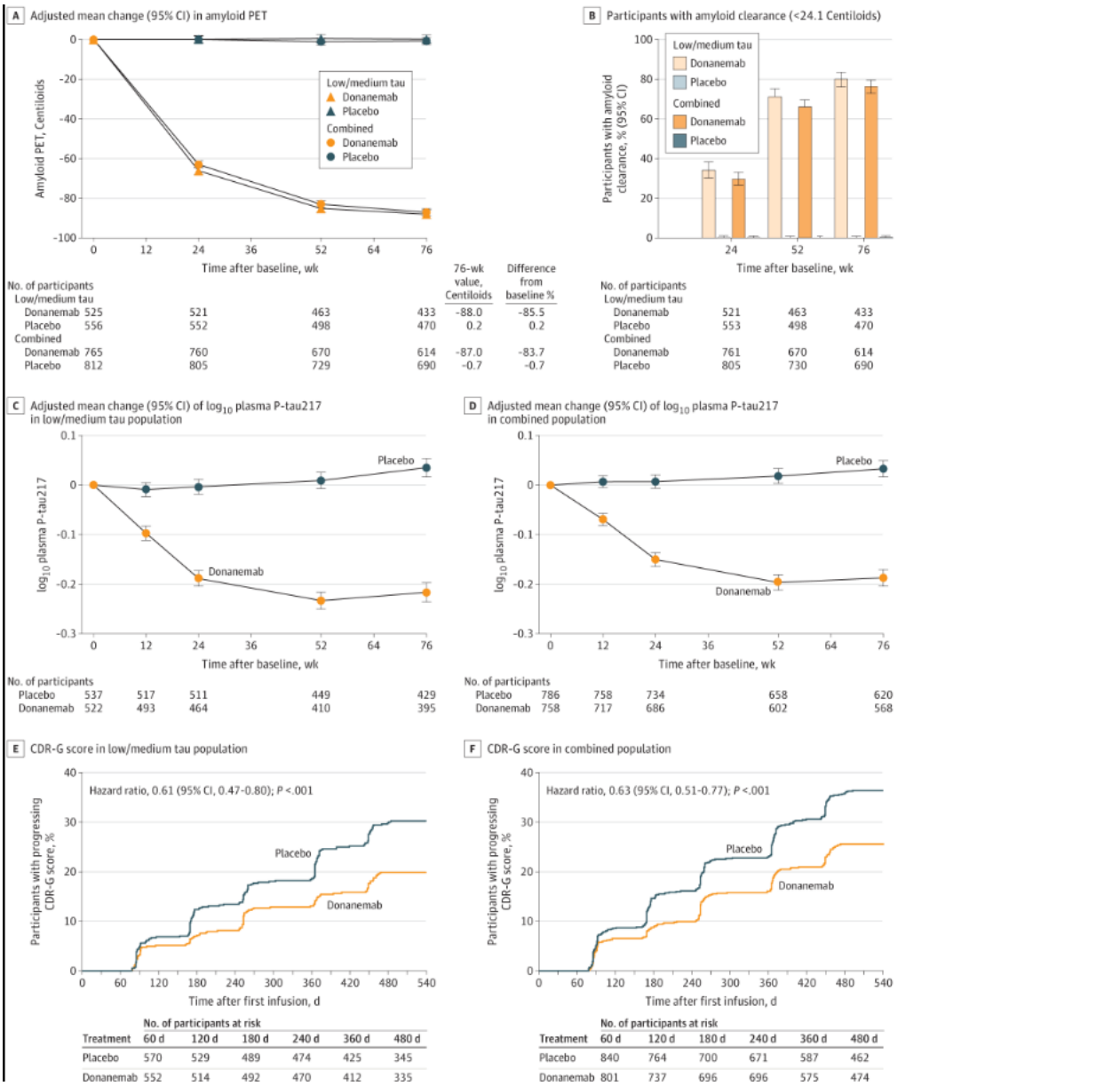
Figure 4. Integrated Alzheimer Disease Rating Scale (iADRS) and Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB) From Baseline to 76 Weeks



A, 35.1% slowing (95% CI, 19.90%-50.23%) of clinical progression. B, 22.3% slowing (95% CI, 11.38%-33.15%) of clinical progression. C, 36.0% slowing (95% CI, 20.76%-51.15%) of clinical progression. D, 28.9% slowing (95% CI, 18.41%-39.44%) of clinical progression. iADRS data were analysed using the natural cubic spline model with 2 degrees of freedom (NCS2) and CDR-SB data were analysed with mixed models for repeated measures (MMRM). For MMRM analyses, 95% CIs for least-squares mean changes were calculated with the normal approximation method. For the Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living, 13-item cognitive subscale of the Alzheimer Disease Assessment Scale, and CDR-SB clinical assessments analysed with NCS2, see eFigure 1 (low/medium tau population) and eFigure 2 (combined population) in Supplement 3 and Table 2. For all clinical assessments analysed with MMRM, see eFigure 3 (low/medium tau population) and 4 (combined population) in Supplement 3 and Table 2. P < .001 for all 76 week time points.

At 76 weeks, brain amyloid plaque level decreased by 88.0 Centiloids (95% CI, −90.20 to −85.87) with donanemab treatment and increased by 0.2 Centiloids (95% CI, −1.91 to 2.26) in the placebo group in the low/medium tau population; in the combined population, amyloid plaque level decreased by 87.0 Centiloids (95% CI, −88.90 to −85.17) with donanemab treatment and decreased by 0.67 Centiloids (95% CI, −2.45 to 1.11) in the placebo group (Figure 3A). The percentages of donanemab-treated participants in the low/medium tau population who reached amyloid clearance were 34.2% (95% CI, 30.22%-38.34%) at 24 weeks and 80.1% (95% CI, 76.12%-83.62%) at 76 weeks compared with 0.2% (95% CI, 0.03%-1.02%) at 24 weeks and 0% (95% CI, 0.00%-0.81%) at 76 weeks of placebo-treated participants. In the combined population, amyloid clearance was reached in 29.7% (95% CI, 26.56%-33.04%) of participants at 24 weeks and 76.4% (95% CI, 72.87%-79.57%) at 76 weeks of donanemab-treated participants compared with 0.2% (95% CI, 0.07%-0.90%) at 24 weeks and 0.3% (95% CI, 0.08%-1.05%) at 76 weeks of placebo-treated participants (Figure 3B).

Figure 5. Brain Amyloid, Plasma Phosphorylated Tau 217 (P-tau217), and Hazard Ratios for Risk of Disease Progression



Biomarker data shown were analysed using mixed models for repeated measures (MMRM). For MMRM analyses, 95% CIs for the least-squares mean changes were calculated with the normal approximation method. P < .001 for all time points in panels A-D. B, P value is from Fisher exact test comparing the percent amyloid negative by treatment groups at each visit. E and F, The analysis was conducted using a Cox proportional hazards model. There were 163 events among 573 participants in the placebo group and 100 events among 555 participants in the donanemab group in the low/medium tau population and 288 events among 844 participants in the placebo group and 186 events among 805 participants in the donanemab group in the combined population. CDR-G indicates Clinical Dementia Rating Global Score.

AUTHORS' CONCLUSIONS

Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology population.

Mintun et al., 2021. Donanemab in Early Alzheimer's Disease (Funded by Eli Lilly; TRAILBLAZER-ALZ Clinical- Trials.gov number, NCT03367403.)

This was a phase 2 trial of donanemab in patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on positron-emission tomography (PET).

Patient selection included flortaucipir (max SUVR of 1.46) and florbetapir (SUVR ≥1.17, equivalent to 37 centiloids) PET examinations. The flortaucipir and florbetapir PET scans were reviewed at a centralized PET imaging facility for assessment of eligibility.

Patients were randomly assigned in a 1:1 ratio to receive donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo intravenously every 4 weeks for up to 72 weeks. In participants who were treated with donanemab, if the amyloid plaque level as assessed by florbetapir PET (performed at 24 and 52 weeks) was 11 to less than 25 centiloids, considered to indicate removal of amyloid plaques, the dose was lowered to 700 mg. If the amyloid plaque level was less than 11 centiloids on any one scan or was 11 to less than 25 centiloids on two consecutive scans, donanemab was switched to placebo. Final safety and efficacy assessments were performed at 76 weeks, 4 weeks after the last infusion.

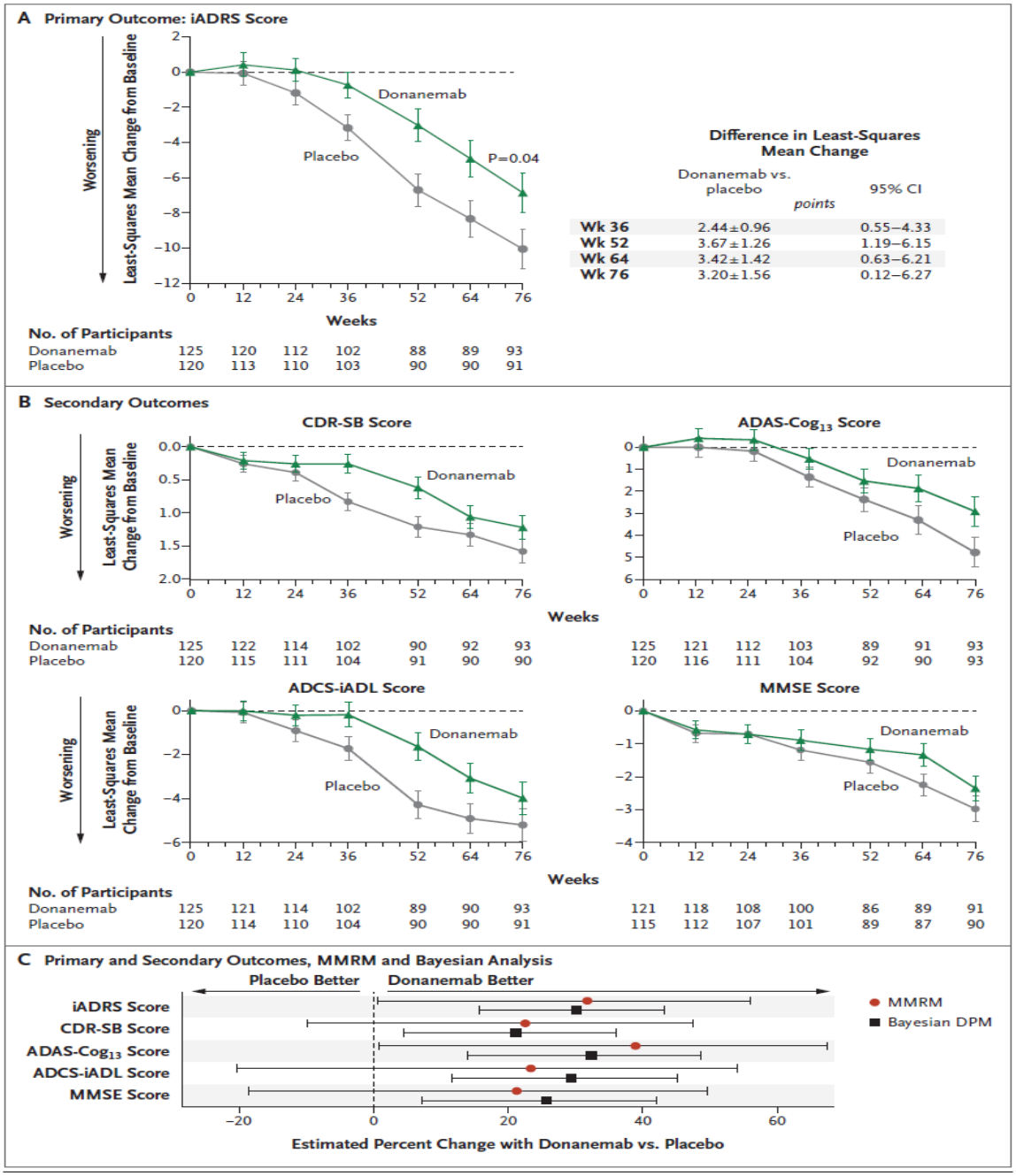
The primary outcome was the change from baseline in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; range, 0 to 144, with lower scores indicating greater cognitive and functional impairment) at 76 weeks. Secondary outcomes included the change in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog13), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), and the Mini–Mental State Examination (MMSE), as well as the change in the amyloid and tau burden on PET.

RESULTS

Of the 1955 patients assessed for eligibility, 257 were enrolled in the trial; 131 were assigned to receive donanemab and 126 to receive placebo. The treatment arms were fairly well balanced at the baseline. In the donanemab and placebo groups, the mean age was 75.0 and 75.4 years, respectively; 51.9% and 51.6% were women, 93.1% and 96.0% were White, and 72.5% and 74.2% were APOE ε4 carriers. The mean baseline iADRS score was 106.2 in the donanemab group and 105.9 in the placebo group, the MMSE score 23.6 and 23.7, the CDR-SB score 3.6 and 3.4, the global tau load on flortaucipir PET 0.47 and 0.46, and the amyloid plaque level on florbetapir PET 107.6 and 101.1 centiloids.

The change from baseline in the iADRS score at 76 weeks was −6.86 with donanemab and −10.06 with placebo (difference, 3.20; 95% confidence interval, 0.12 to 6.27; P = 0.04), smaller decrease indicating less cognitive and functional decline. The results for most secondary outcomes showed no substantial difference.

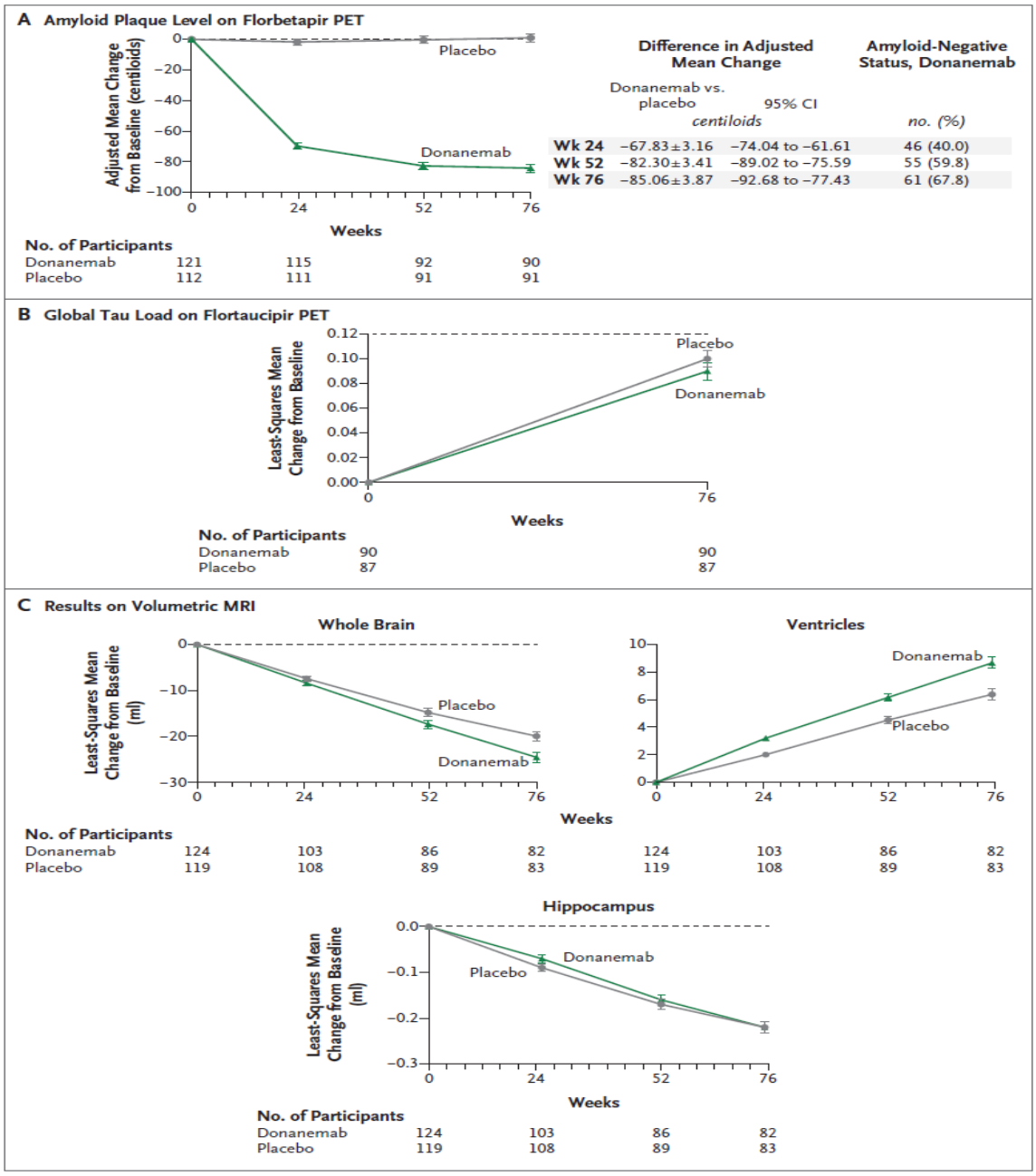
Figure 6. Primary and Secondary Clinical Outcomes



Panel A shows the results for the primary outcome, the least-squares mean change from baseline to 76 weeks in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; scores range from 0 to 144, with lower scores indicating a greater cognitive deficit and greater impairment of the ability to perform activities of daily living), in the donanemab group and the placebo group, analyzed with a mixed model for repeated measures (MMRM). The difference between the donanemab group and the placebo group in the primary outcome was 3.20 (95% confidence interval [CI], 0.12 to 6.27; P=0.04). Panel B shows the results for secondary clini- cal outcomes, including the least-squares mean change from baseline to 76 weeks in scores on the Clinical De- mentia Rating Scale–Sum of Boxes (CDR-SB; scores range from 0 to 18, with higher scores indicating great- er impairment), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog_{13}; scores range from 0 to 85, with higher scores indicating a greater deficit), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL; scores range from 0 to 59, with lower scores indicating greater impairment), and the Mini– Mental State Examination (MMSE; scores range from 0 to 30, with higher scores indicating better mental performance), in the donanemab group and the place- bo group, analyzed with the MMRM. Panel C shows the estimated percent change in the iADRS, CDR-SB, ADAS-Cog_{13}, ADCS-iADL, and MMSE scores in the donanemab group as compared with the placebo group, analyzed with the MMRM at 76 weeks (with 95% confi- dence intervals) and with the Bayesian disease progres- sion model (DPM) over the entire 18-month intervention period (with 95% credible intervals). The credible intervals for data in the Bayesian disease progression model were not adjusted for multiple comparisons, and no definite conclusions can be drawn. Plus–minus values are means ±SE. I bars indicate standard errors.

At 76 weeks, the reduction in the amyloid plaque level as assessed by florbetapir PET was 85.06 centiloids greater in the donanemab group than in the placebo group (−84.13 vs. 0.93 centiloids) (Fig. A). The percentage of participants in the donanemab group who had amyloid-negative status (defined as an. amyloid plaque level of <24.10 centiloids) at 24, 52, and 76 weeks was 40.0%, 59.8%, and 67.8%, respectively (Fig. 3A). In addition, approximately 27.4% and 54.7% of participants in the donanemab group had sufficient lowering of the amyloid plaque level to switch to placebo infusion at 28 and 56 weeks, respectively. Evaluation of the change from baseline to 76 weeks in the global tau load as assessed by flortaucipir PET did not show a substantial difference between groups (Fig. B), nor did evaluation of the change in hippocampal volume as assessed by volumetric MRI (Fig. C). At 52 and 76 weeks, volumetric MRI showed a greater decrease in whole-brain volume and a greater increase in ventricular volume in the donanemab group than in the placebo group (Fig. C).

Figure 7. Secondary Biomarker Outcomes



Results are shown for secondary biomarker outcomes, including the change from baseline to 76 weeks in the level of amyloid plaques deposited in the brain as assessed by positron-emission tomography (PET) with injection of ^{18}F-florbetapir (Panel A), in the global tau load as assessed by PET with injection of ^{18}F-flortaucipir (Panel B), and in the whole-brain volume, ventricular volume, and hippocampal volume as assessed by volumetric magnetic resonance imaging (MRI) (Panel C). Amyloid-negative status is defined as an amyloid plaque level of less than 24.10 centiloids, which is the average level among otherwise healthy persons of a similar age. Plus–minus values are means ±SE. I bars indicate standard errors.

van Dyck et al. 2023. Lecanemab in Early Alzheimer's Disease (Funded by Eisai and Biogen; Clarity AD ClinicalTrials.gov number, NCT03887455.)

This was an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing.

The trial included participants 50 to 90 years of age, with either mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease–related dementia on the basis of National Institute on Aging–Alzheimer's Association criteria (Albert et al., 2011; McKhann et al., 2011). Amyloid positivity was determined by PET or CSF measurement of Aβ1–42. All the participants had objective impairment in episodic memory as indicated by at least 1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV–Logical Memory II.

Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo.

The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change from baseline at 18 months in the following: amyloid burden on PET as measured in centiloids (with either florbetaben, florbetapir, or flutemetamol tracers) in a substudy, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90, with higher scores indicating greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97, with higher scores indicating greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53, with lower scores indicating greater impairment). Biomarker assessments included CSF biomarkers (Aβ1–40, Aβ1–42, total tau, phosphorylated tau 181 [p-tau181], neurogranin, and neuro- filament light chain [NfL]) and plasma biomarkers (Aβ42/40 ratio, p-tau181, glial fibrillary acidic protein [GFAP], and NfL). Tau PET and volumetric magnetic resonance imaging (MRI) results were not been fully analysed.

During the trial, participants underwent serial blood testing for plasma biomarkers and could participate in three optional substudies that evaluated longitudinal changes in brain amyloid burden as measured by positron- emission tomography (PET), brain tau pathologic features as measured by PET, and cerebro- spinal fluid (CSF) biomarkers of Alzheimer's disease.

RESULTS

From the 5967 persons screened a total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The population across the treatment arms was well balanced. Enrolment in three longitudinal substudies included 698 participants in the substudy of amyloid burden on PET, 257 in the study of tau pathologic features on PET, and 281 in the substudy of CSF biomarkers of Alzheimer's disease.

Populations at baseline across various substudies and across treatment arms were fairly well balanced.

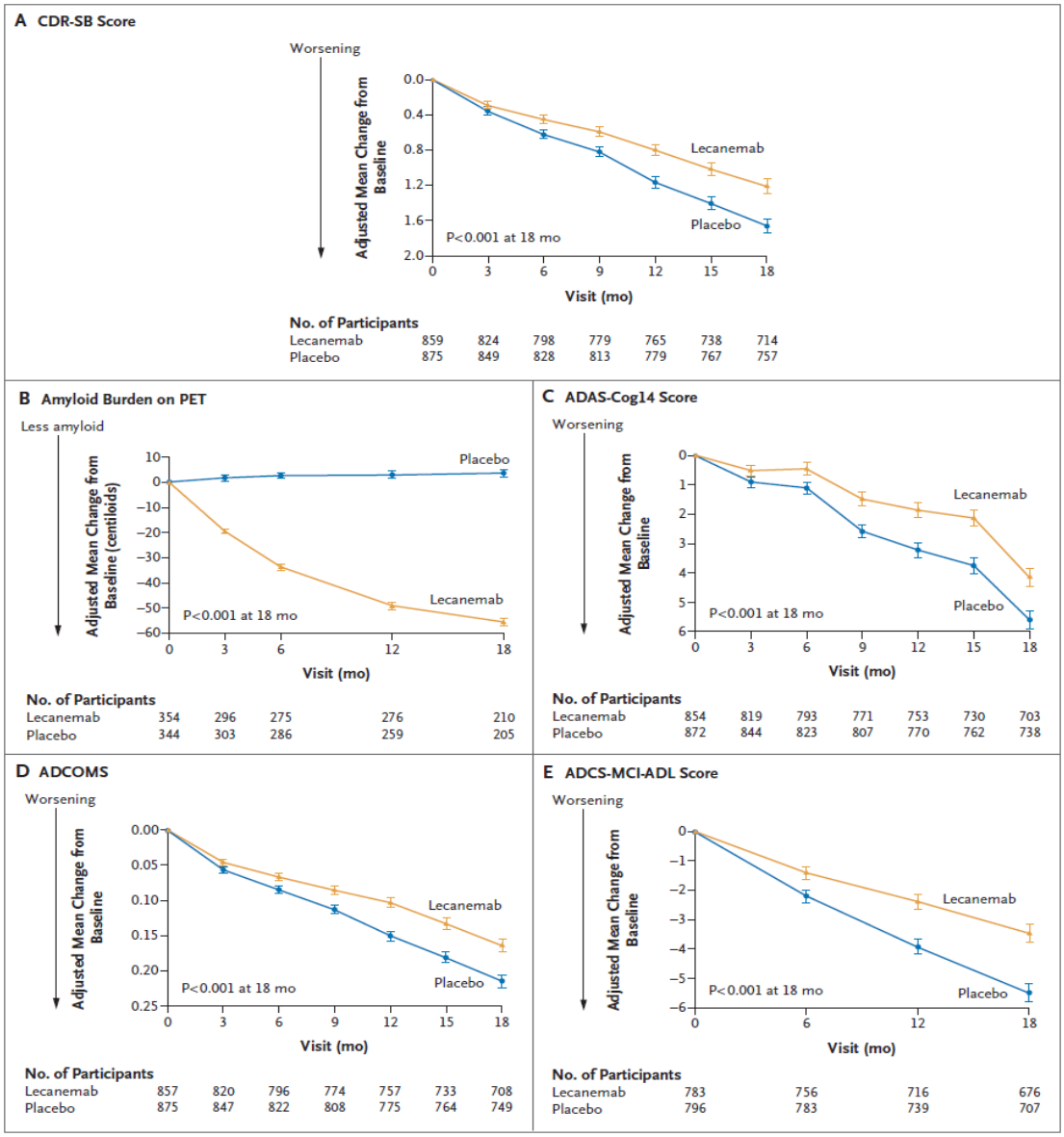
The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001).

In the substudy with PET the patients had 77.92±44.84 (range: −16.6 to 213.2) and 75.03±41.82 (range: −17.0 to 179.6) centiloids on amyloid PET in the lecanemab and placebo arms respectively. In this population there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, −59.1 centiloids; 95% CI, −62.6 to −55.6) as measured by means of centiloid. Other mean differences between the two groups in the change from baseline favouring lecanemab were as follows: for the ADAS-cog14 score, −1.44 (95% CI, −2.27 to −0.61; P<0.001); for the ADCOMS, −0.050 (95% CI, −0.074 to −0.027; P<0.001); and for the ADCS-MCI-ADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001).

After 18 months of treatment in the amyloid PET substudy, the mean amyloid level of 22.99 centiloids in the lecanemab group was reported.

The Authors state that in the CSF substudy and in plasma analyses involving the overall population, markers of amyloid, tau, neurodegeneration, and neuroinflammation (plasma GFAP) were reduced to a greater extent with lecanemab than with placebo, with the exception of NfL. No data are presented in the publication.

Figure 8. Key study results - efficacy



AUTHORS' CONCLUSIONS

Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease.

Budd Haeberlein et al. 2022. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

The publication describes post-hoc analysis of biomarkers in accordance with the pre-specified analysis plan of the two randomized, double-blind, placebo-controlled, global, phase 3 studies (EMERGE -

NCT02484547 and ENGAGE - NCT02477800) of aducanumab in patients with early Alzheimer's disease which were stopped prematurely due to futility.

SETTING: These studies involved 348 sites in 20 countries.

PARTICIPANTS: Participants were 1638 (EMERGE) and 1647 (ENGAGE) patients (aged 50–85 years, confirmed amyloid pathology) who met clinical criteria for mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia, of which 1812 (55.2%) completed the study.

INTERVENTION: Participants were randomly assigned 1:1:1 to receive aducanumab low dose (3 or 6 mg/kg target dose), high dose (10 mg/kg target dose), or placebo via IV infusion once every 4 weeks over 76 weeks.

MEASUREMENTS: The primary outcome measure was change from baseline to week 78 on the Clinical Dementia Rating Sum of Boxes (CDR-SB), an integrated scale that assesses both function and cognition. Other measures included safety assessments; secondary and tertiary clinical outcomes that assessed cognition, function, and behaviour; and biomarker endpoints.

Longitudinal amyloid PET imaging using 18F-florbetapir was performed in a subset of patients (n=488 in EMERGE; n=585 in ENGAGE) at screening, week 26, and week 78. The cortical composite standardized uptake value ratio (SUVR) was derived (Savigny et al., 2016, Ostrowski et al., 2012). The composite SUVR was also transformed to centiloid (CL) units (Klunk et al., 2015).

Longitudinal tau PET imaging using 18F-MK-6240 was performed in a subset of patients (n=37, pooled across studies) at both screening and week 78. Due to early termination of the studies, the median postbaseline visit occurred at 13.6 months (range, 9.5 to 19.6 months).

Cerebrospinal fluid (CSF) was collected at both baseline and week 78 in a subset of patients (n=78 in EMERGE; n=53 in ENGAGE). CSF levels of Aß1-42, phosphorylated tau181 (p-tau), and total tau (t-tau) were measured using the Lumipulse G immunoassays (Fujirebio).

Lumbar puncture was used to collect CSF samples from living clinical trial CSF substudy participants with early AD via a 22g Sprotte atraumatic needle inserted between the L3/L4 or L4/L5 interspace. Time of collection was recorded. Samples were collected at room temperature following usual and customary sterile techniques and stored in polypropylene tubes at -70°C for 7 to 52 months until analysis.

At week 78, the effects of aducanumab treatment on plasma-tau181 levels were assessed in clinical trial participants with early AD. A 6-mL tube of whole blood was collected using a K2EDTA tube and processed according to standard procedures with centrifugation at room temperature to separate cells and plasma within 1 hour of sample collection. Following centrifugation, samples were aliquoted into 2-mL polypropylene tubes and frozen immediately at -70°C until shipment (except where unavailable, in which case samples were stored at -20°C). Samples were stored buffer-free between -70°C and -80°C until analysis for approximately 6 years. Only the intent-to-treat (ITT) patients with plasma samples available at both screening and week 78 were selected for further analyses. Available samples at screening, week 56 (week 48 if under PV1–3), and week 78 were tested. A total of 6684 plasma samples (n=3474 from EMERGE and n=3210 from ENGAGE) were analyzed using the Quanterix Simoa p-tau181 Advantage V2 kit at Frontage Laboratories' (Exton, PA) CLIA laboratory. Data were captured by the Quanterix Simoa HD-X Analyzer. Watson LIMS Version 7.6 was used for data regression. The standard curve was fitted with a four-parameter logistic (Marquardt) regression model with a weighting factor of 1/Y2. Concentration was presented in pg/mL, and coefficient of variation (CV) and relative error (RE) as percentages. The inter-assay CV was 6.49-8.15%, and the intra-assay CV was 8.30-9.21%.

Change from baseline in amyloid PET composite SUVR was analyzed using an MMRM with fixed effects of treatment, categorical visit, treatment-by-visit interaction, baseline SUVR, baseline SUVR-by-visit interaction, baseline MMSE score, ApoE c4 status (carrier and noncarrier), and baseline age.

MMRM analyses were also conducted to assess the effect of aducanumab on change from baseline in plasma p-tau181 levels (using data from the placebo-controlled period; fixed effects included visit, treatment group and its interaction with visit, baseline value and its interaction with visit, age, and ApoE c4 status. Correlation analyses were conducted to assess the following: 1) relationship between change from baseline in plasma p-tau181 levels and amyloid PET composite SUVR (assessed in three pooled treatment arms); 2) relationship between change from baseline in plasma p-tau181 levels and clinical decline (assessed in pooled low- and high-dose arms). Data were presented using partial Spearman correlation coefficients adjusting for baseline plasma p-tau181 levels, baseline amyloid PET SUVR (for 1) or baseline clinical scores (for 2), and age.

Tau PET SUVR and CSF biomarkers were analysed using analysis of covariance models.

All biomarker analyses were exploratory; amyloid PET was the only biomarker outcome for which a sample size calculation was performed.

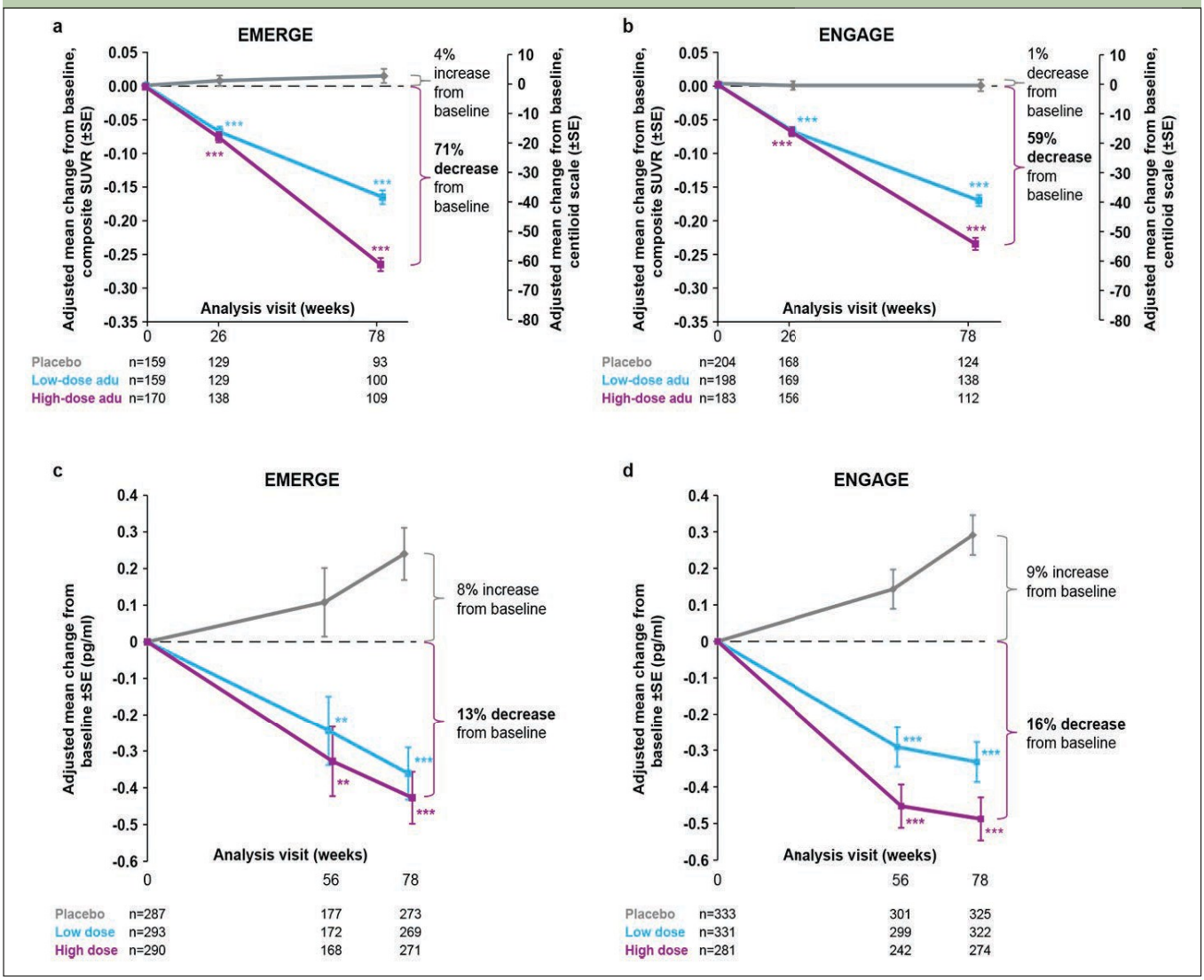
RESULTS: EMERGE and ENGAGE were halted based on futility analysis of data pooled from the first approximately 50% of enrolled patients; subsequent efficacy analyses included data from a larger data set collected up to futility declaration and followed prespecified statistical analyses. The primary endpoint was met in EMERGE (difference of -0.39 for high- dose aducanumab vs placebo [95% CI, -0.69 to -0.09; P=.012; 22% decrease]) but not in ENGAGE (difference of 0.03, [95% CI, -0.26 to 0.33; P=.833; 2% increase]).

Amyloid PET substudies assessed n=488 and n=585 patients in EMERGE and ENGAGE, respectively. These substudies showed a dose- and time-dependent reduction in amyloid PET SUVR in both EMERGE and ENGAGE. At week 78, the difference in adjusted mean change from baseline between high-dose aducanumab and placebo was -0.278 (95% CI, -0.306 to -0.250; P<.0001) for EMERGE (Fig. 2a) and -0.232 (95% CI, -0.256 to -0.208; P<.0001) for ENGAGE (Fig. 2b). For the high-dose aducanumab arm, the reduction in adjusted mean change from baseline in amyloid PET SUVR in ENGAGE was 16.5% less than that in EMERGE at week 78. The adjusted mean changes from baseline in amyloid PET SUVR for low-dose aducanumab arms were similar.

Plasma p-tau was assayed in 870 and 945 patients in EMERGE and ENGAGE, respectively. An increase over time in plasma p-tau181 levels, was observed in the placebo groups of both EMERGE (Fig. 2c) and ENGAGE (Fig. 2d). In the treatment arms, reductions in plasma p-tau181 levels were observed over time. The difference in adjusted mean change from baseline between high-dose aducanumab and placebo was -0.667 (95% CI, -0.860 to -0.474; P<.0001) for EMERGE and -0.777 (95% CI, -0.931 to -0.623; P<.0001) for ENGAGE. More modest decreases were observed in the low-dose aducanumab groups.

Figure 9. Longitudinal change from baseline in amyloid PET (composite SUVR and centiloid) and plasma p-tau181

Figure 9. Longitudinal change from baseline in amyloid PET (composite SUVR and centiloid) and plasma p-tau[181]



Longitudinal change from baseline in amyloid PET composite SUVR (and centiloid) assessed by 18F-florbetapir in the amyloid PET substudies of EMERGE (a) and ENGAGE (b). In panels (a) and (b), percentages from baseline are based on the centiloid scale. The composite SUVR was computed from the frontal, parietal, lateral temporal, sensorimotor, anterior, and posterior cingulate cortices and normalized using the cerebellum as the reference region. Longitudinal change from baseline in plasma p-tau181 levels in the plasma p-tau181 analysis populations from EMERGE (c) and ENGAGE (d); **P<.01 *** P<.001. Error bars denote SE; adu, aducanumab; PET, positron emission tomography; SUVR, standardized uptake value ratio.

After 78 weeks, 48% of patients from EMERGE and 31% of patients from ENGAGE treated with high-dose aducanumab had a PET composite SUVR score of 1.10, a proposed threshold that is reported to distinguish between Aß-negative and -positive patients (Joshi et al., 2015). Notably, the %-ages have been calculated based on the evaluated population at the time point of interest (not considering overall population studied) without imputation.

Figure 10. Proportion of patients in EMERGE and ENGAGE with amyloid PET composite SUVR ***≤1.10*** *at week 78 (supplemental Table 4)*

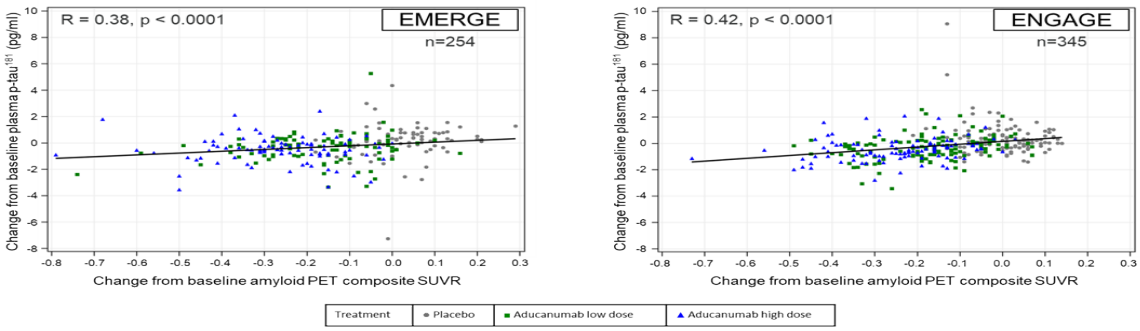
	EMERGE			ENGAGE		
	Placebo (n=159)	**Low dose** (n=159)	**High dose** (n=170)	**Placebo** (n=204)	**Low dose** (n=198)	**High dose** (n=183)
Baseline, n (%)						
Number evaluable	159 (100)	159 (100)	170 (100)	204 (100)	198 (100)	183 (100)
Amyloid PET composite SUVR ≤1.10	10 (6)	10 (6)	9 (5)	17 (8)	16 (8)	9 (5)
Week 26, n (%)						
Number evaluable	129 (100)	129 (100)	138 (100)	168 (100)	169 (100)	156 (100)
Amyloid PET composite SUVR ≤1.10	6 (5)	9 (7)	10 (7)	18 (11)	15 (9)	11 (7)
Week 78, n (%)						
Number evaluable	93 (100)	100 (100)	109 (100)	124 (100)	138 (100)	112 (100)
Amyloid PET composite SUVR ≤1.10	5 (5)	15 (15)	52 (48)	10 (8)	29 (21)	35 (31)

In both EMERGE and ENGAGE, reductions in plasma p-tau181 levels were positively (low level of correlation) correlated with reductions in amyloid PET SUVR at week 78 (Supplemental Data Fig below; panel a).

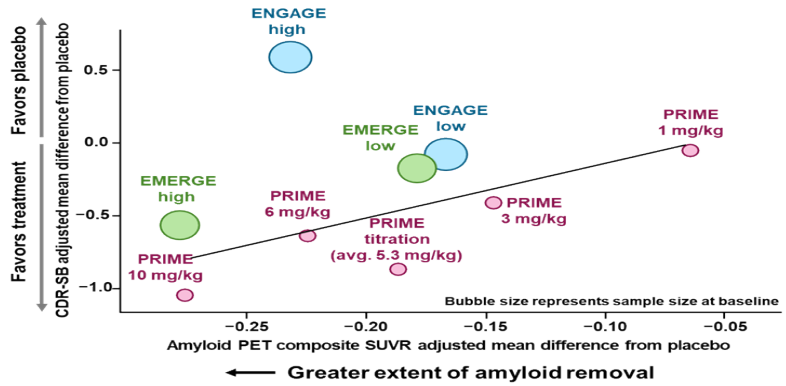
Correlation analyses showed a correlation in the hypothesized direction between plasma p-tau181 levels and clinical efficacy outcomes in both studies, but level of correlation was very low. Similar correlation analysis between the clinical treatment effects and Aß PET were inconsistent across the studies, various clinical parameters and against the hypothesized direction (Supplemental Data Fig. Panel b).

Figure 11. Correlation analysis of amyloid PET, plasma p-tau181 and clinical efficacy (Supplemental data)

a



b



c

Association between change in Aβ PET composite SUVR at week 78		Hypothesized correlation	EMERGE Correlation (95% CI) (n=182-185)	ENGAGE Correlation (95% CI) (n=240)
	CDR-SB	Positive	**0.19**** (0.048,0.327)	−0.06 (−0.182,0.071)
	MMSE	Negative	**−0.24***** (−0.374, −0.101)	0.05 (−0.078,0.176)
	ADAS-Cog13	Positive	**0.20**** (0.056,0.336)	0.09 (−0.038,0.215)
	ADCS-ADL-MCI	Negative	**−0.29***** (−0.421, −0.153)	0.02 (−0.103,0.152)
Association between change in p-tau181 and efficacy at Week 78		**Hypothesized correlation**	**EMERGE Correlation (95% CI) (n=514-521)**	**ENGAGE Correlation (95% CI) (n=577-581)**
	CDR-SB	Positive	**0.11*** (0.019, 0.190)	**0.14***** (0.063, 0.223)
	MMSE	Negative	**-0.21***** (-0.286, -0.121)	**-0.15***** (-0.231, -0.071)
	ADAS-Cog13	Positive	**0.17***** (0.081, 0.250)	**0.15***** (0.074, 0.234)
	ADCS-ADL-MCI	Negative	**-0.12**** (-0.201, -0.030)	**-0.14**** (-0.217, -0.056)

Panel a shows scatterplot of change from baseline in plasma p-tau181 levels vs. change from baseline in amyloid PET composite SUVR at Week 78 in EMERGE (left) and ENGAGE (right). R: Partial spearman correlation adjusted for baseline p-tau, baseline amyloid PET, and age. Correlations calculated based on all arms.

Panel b shows association between treatment effect on brain Aβ plaque levels and CDR-SB across aducanumab studies (group-level analysis). The analysis was conducted in active treatment groups, as pre-specified. CDR-SB results for EMERGE and ENGAGE were from the PET substudies using the same mixed model for repeated measures as the primary analysis for CDR-SB. The regression line was derived based on the data points from all three studies except the ENGAGE high-dose group. Sample sizes for each study are as follows: EMERGE (n=159 for low dose; n= 170 for high dose); ENGAGE (n=198 for low dose; n=183 for high dose); PRIME (n=29 for 1 mg/kg; n=32 for 3 mg/kg; n=30 for 6 mg/kg; n=31 for 10 mg/kg; n=19 for titration).

Panel c shows correlations between amyloid reduction or reduction in levels of plasma p-tau181 and efficacy endpoints change from baseline at week 78 (participant-level analysis). The population is limited to those participants in the amyloid PET or plasma p-tau181 subgroup who completed amyloid PET assessment or collection of plasma p-tau181 and efficacy assessments at week 78. P values (nominal): *P<.05 ** P<.01, *** P<.001. Correlations are partial Spearman correlations assessed in pooled low- and high-dose groups after adjustment for baseline biomarker and efficacy values (and age for correlation between plasma p-tau181 and efficacy correlation).

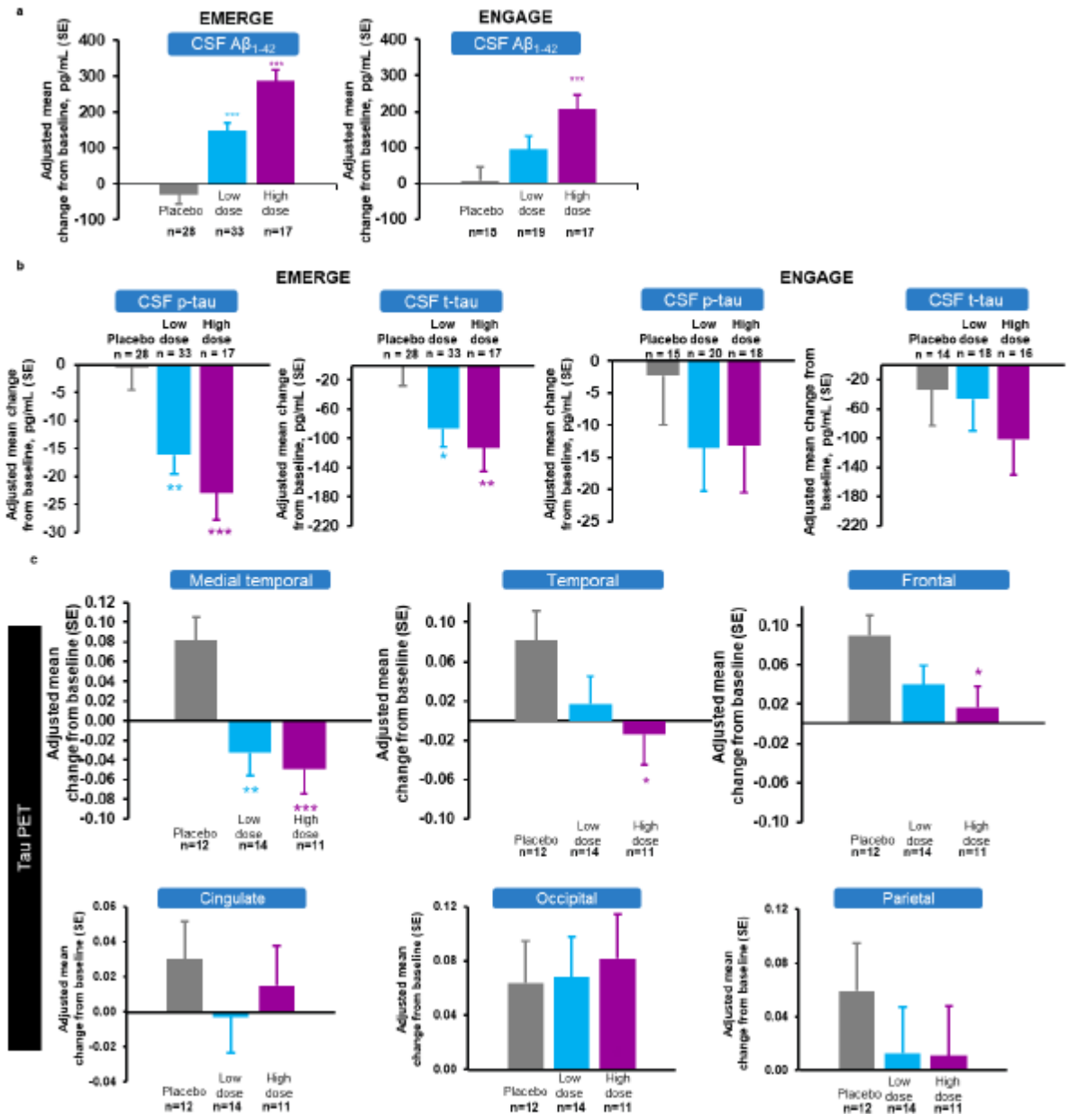
Aβ, amyloid β; ADAS-Cog13, Alzheimer's Disease Assessment Scale–cognitive subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, avg, average; mild cognitive impairment version; CDR-SB, Clinical Dementia Rating Scale–sum of boxes; MMSE, Mini Mental State Examination; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.

In the EMERGE and ENGAGE CSF substudies, a dose-dependent increase in CSF Aß1-42 and a dose-dependent decrease in CSF p-tau and t-tau levels was observed in EMERGE; in ENGAGE, CSF Aß1-42 level was increased in the high-dose group, while a numerical decrease was observed in the high-dose group for CSF p-tau and t-tau levels. (Supplemental Figure below; Panel a)

Pooled results from EMERGE and ENGAGE showed a reduction in tau PET signal on high-dose aducanumab compared to placebo and low-dose in the medial temporal, temporal, and frontal lobes (Supplemental Fig. 5c). The remaining brain regions showed no dose-dependency (parietal region), inconsistent results (cingulate) or increased signal than on placebo (Occipital).

The effect of aducanumab on structural MRI, a measure of neurodegeneration, was also assessed. A significant increase in the change from baseline to week 30 and week 78 in MRI lateral ventricle volume was observed in aducanumab treatment groups (low- and high-dose groups in both EMERGE and ENGAGE) relative to placebo (P<.0001); no effects related to treatment were observed in measures for hippocampus and whole brain).

Figure 12. Exploratory biomarker results from EMERGE and ENGAGE



Panel a shows adjusted mean change from baseline in CSF Aβ1-42 values in the CSF substudy for EMERGE (left) and ENGAGE (right). Results were based on an analysis of covariance model at week 78, fitted with change from baseline as the dependent variable, and with treatment, baseline CSF Aβ1-42 value, baseline age, and laboratory ApoE ε4 status (carrier and noncarrier) as the independent variables. Panel b shows adjusted mean change from baseline in CSF levels of p-tau and t-tau in the CSF substudy for EMERGE (left two panels) and ENGAGE (right two panels). Results were based on an analysis of covariance model at week 78, fitted with change from baseline as the dependent variable, and with treatment, baseline biomarker value, baseline age, and laboratory ApoE ε4 status (carrier and noncarrier) as the independent variables. Panel c shows aducanumab treatment effect on tau PET SUVR (pooled results from EMERGE and ENGAGE) in the medial temporal (top left), temporal (top middle), afrontal (top right), cingulate (bottom left), occipital (bottom middle), and parietal (bottom right) regions. Adjusted mean change from baseline in tau PET average standardized uptake value ratio was assessed by 18F-MK-6240 in the tau PET substudy. Results were based on an analysis of covariance model at week 78, fitted with change from baseline as the dependent variable, and with categorical treatment, baseline tau PET value, and laboratory ApoE ε4 status (carrier and noncarrier) as independent variables.

AUTHORS' CONCLUSIONS: Data from EMERGE demonstrated a statistically significant change across all four primary and secondary clinical endpoints. ENGAGE did not meet its primary or secondary endpoints. A dose- and time-dependent reduction in pathophysiological markers of Alzheimer's disease was observed in both trials.

Lowe et al. 2021: Donanemab (LY3002813) Phase 1b Study in Alzheimer's Disease: Rapid and Sustained Reduction of Brain Amyloid Measured by Florbetapir F18 Imaging

This was a 3-part, patient- and investigator-blind, randomized within cohort, placebo-controlled, parallel-group, single and multiple-dose Phase 1b study to assess effects of donanemab on brain amyloid plaque load after single and multiple intravenous doses, as well as pharmacokinetics, safety/tolerability, and immunogenicity in the patients with mild cognitive impairment (MCI) due to AD and mild to moderate AD.

Overall goal of this study was to determine whether different dosing regimens (single-dose, dosing frequency, and chronic dosing for maximal PD effect) could mitigate immunogenicity, potential immune safety issues and produce sustained amyloid reduction.

Amyloid plaque-positive patients (N=61 and 6 cohorts) with MCI due to Alzheimer's disease and mild-to moderate Alzheimer's disease dementia were treated with donanemab administered as i.v. single dose 10-, 20- or 40- mg/kg (N = 18), multiple doses of 10-mg/kg every 2 weeks for 24 weeks (N = 10), and 10- or 20-mg/kg every 4 weeks for 72 weeks (N=18) or placebo (N =15).

Mild cognitive impairment was defined by means of memory impairment on the Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR, picture version; <27 for free recall), a Mini–Mental State Examination (MMSE) score of 16 to 30, a Clinical Dementia Rating (CDR) of 0.5 to 2 and memory box score ≥0.5.

A florbetapir PET scan consistent with the presence of amyloid pathology (as determined using visual assessments and composite standardized uptake value ratio [SUVr] cut-points [cut-points not specified in the publication]) was required at baseline. The florbetapir F 18 interpretation method used for the eligibility decision included quantification as an adjunct to a visual assessment. The PET imaging core lab was responsible for performing both visual and quantitative analysis of the florbetapir F 18 images (blinding and number of image readers is not specified in the publication).

Florbetapir PET scan was conducted at baseline and at 12, 24, 36, 48, and 72 weeks after starting treatment to estimate mean change in amyloid plaques. Composite SUVr from florbetapir scans were analysed to estimate change (Clark et al., 2011). Furthermore, those SUVr values were converted to the Centiloid scale, a standardized methodology to quantify amyloid burden from PET scans (Navitsky et al., 2018). Florbetapir PET scans in Centiloid units were analysed using a mixed model repeated measure (MMRM) with fixed effects of treatment doses, study visit, interaction between treatment and visit, baseline amyloid PET scan (Centiloid unit), and APOE-ε4 status (carrier /non-carrier) as covariate adjustment. An unstructured covariance matrix was used to model the within-subject variance-covariance errors.

Cognition was assessed at screening or baseline for all patients using the CDR, the MMSE, the FCSRT-IR, the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog-14), the Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living, 24-item questionnaire (ADCS-MCI-ADL-24), and the Neuropsychological test battery (NTB). Additionally, these assessments were also performed at 24, 48, and 72 weeks after starting treatment or at the end of the study (eg, Week 24 for Cohort 3) or upon early discontinuation.

Serum and CSF samples (trough) were evaluated for donanemab.

Based on prior clinical trials conducted by the sponsor, randomizing 6 patients to each donanemab dose was expected to provide approximately 90% power to detect 17% mean florbetapir SUVr reduction of a dose compared to placebo without multiple comparison adjustment.

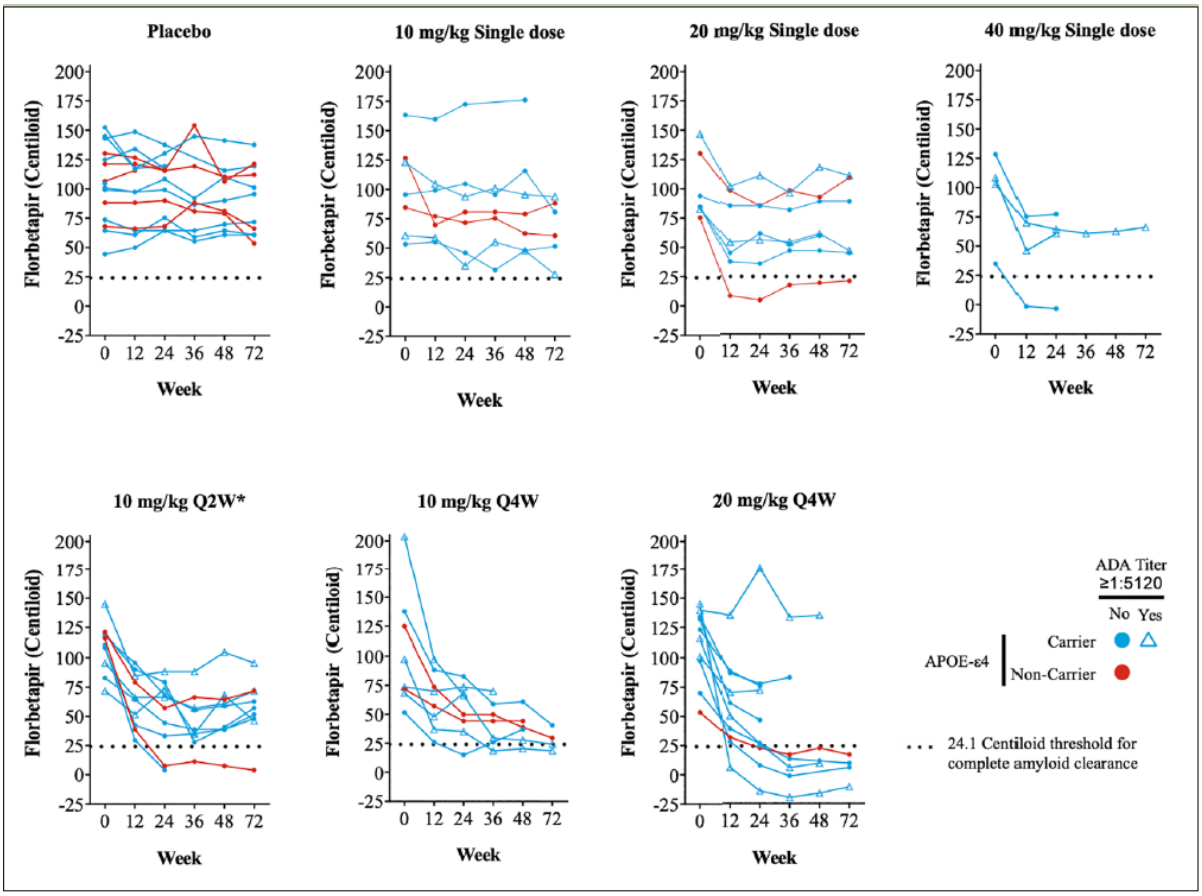
Results: Among 276 patients screened, 61 patients satisfied entry criteria and were enrolled into the study (7, 7, and 4 patients were randomized to the 10-mg/kg, 20-mg/ kg, and 40-mg/kg single dose cohorts respectively; 10 patients were randomized to the 10-mg/kg Q2W for 24 weeks cohort and 8 and 10 patients were randomized to the 10-mg/kg Q4W and 20-mg/kg Q4W cohorts respectively).

For patients receiving at least 1 dose of study drug, the demographic and baseline characteristics were generally balanced across the treatment groups. Patients were male (n =27) and female (n = 34) with a mean age of 73.2 years (range: 54 to 90 years). Forty-three (70.5%) patients were non-Japanese and 18 (29.5%) patients were Japanese. At baseline, the mean MMSE total score was 21.1 (Standard Deviation [SD] = 4.04) and the mean florbetapir PET Centiloid units was 104.5 (SD = 32.77). Seventy-seven percent (47 of 61) of patients were APOE-ε4 carriers (11 homozygotes and 36 heterozygotes).

Main reasons for screen failure were not meeting threshold criteria (Note: threshold not specified, but assumed to be 24.1 Centiloids as defined by Navitsky et al., 2018) for amyloid PET (40 of 154 patients; 26.0%), cognition (MMSE/FCSRTIR; 33 of 154 patients; 21.4%), and microhemorrhage greater than 4 on MRI (16 of 154 patients; 10.4%).

Single dose of 20 mg/kg and all multiple doses of donanemab showed a reduction from baseline in cerebral amyloid (Centiloid units) observed by PET from Week 12 through Week 72 (Figure). Changes were less pronounced on the single dose of 10 mg/kg and 40 mg/kg single dose of donanemab showed decreased uptake of florbetapir, but data are limited to 4 patients and 24 weeks duration, so that

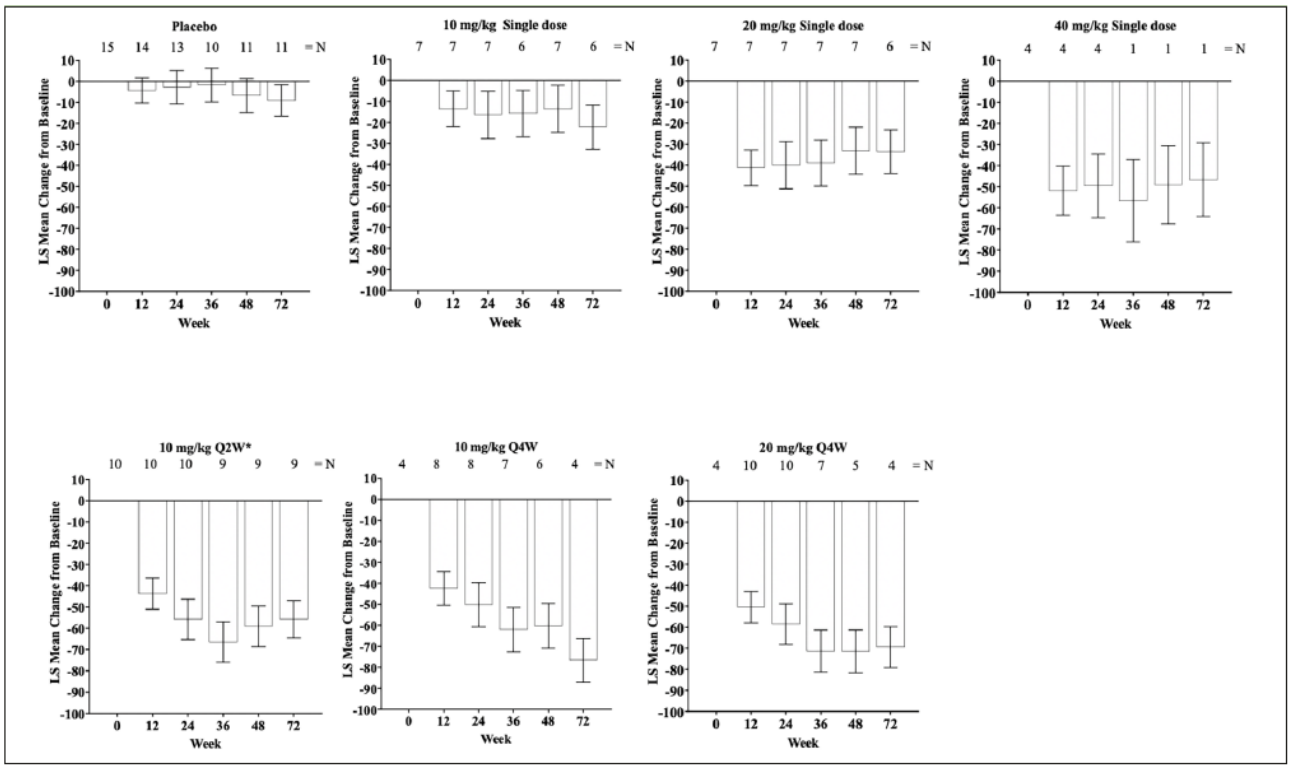
Figure 13. Cerebral amyloid over time as measured by quantitative amyloid PET imaging (florbetapir SUVr). Absolute Centiloid value as calculated from SUVr



*Treatment duration of 24 weeks; Notes: Color indicates APOE-ε4 status and symbol indicates ADA titer of ≥1:5120. The black dashed horizontal line indicates threshold Centiloid value for being amyloid positive; Abbreviations: APOE = apolipoprotein E; LY = LY3002813 (donanemab); PET = positron emission tomography; Q2W = every 2 weeks; Q4W = every 4 weeks; SUVr = standardized uptake value ratio.

At Week 24, amyloid PET least squares mean Centiloid changes from baseline for single donanemab doses were: -16.5 (standard error [SE] = 11.22) 10-mg/kg IV; -40.0 (SE = 11.23) 20-mg/kg IV; and -49.6 (SE = 15.10) 40-mg/kg IV. In contrast, in the placebo group there was no significant reduction in florbetapir PET at 72 weeks (90.9 Centiloids at 72 weeks compared to 104.4 Centiloids at baseline). Corresponding Centiloid changes for multiple doses at Week 24 included: -55.8 (SE = 9.51) 10-mg/kg Q2W; -50.2 (SE = 10.54) 10-mg/kg Q4W; and -58.4 (SE = 9.66) 20-mg/kg Q4W. Patients in the 20 mg/kg Q4W cohort tended to achieve greater plaque reduction earlier in the study than patients in either of the 10 mg/kg multiple dose cohorts (Figures).

Figure 14. LS mean change of florbetapir PET scans from baseline (Centiloid units) through Week 72 following single and multiple dosing of IV donanemab



Error bars = SE; *Treatment duration of 24 weeks; Abbreviations: IV = intravenous; LS mean = least squares mean; N = number of patients; PET = positron emission tomography; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error.

After dosing, a sustained reduction in the PET signal for up to 72 weeks was observed across all single- and multiple-dose cohorts. The change in absolute Centiloid value did not appear to be influenced by APOE-ε4 status with no clear association between presence of the APOE-ε4 allele and florbetapir PET response (Figure). TE-ADAs also appeared not to impact the reduction in amyloid as some participants with high TE-ADA titers (≥1:5120) still had a reduction in amyloid in this study (Figure above).

Overall, 2 participants in single-dose cohorts (1 in 20-mg /kg and 1 in 40-mg /kg) and 9 participants in the multiple-dose cohorts (2 in 10mg/kg Q2W; 2 in 10-mg /kg Q4W; and 5 in 20-mg /kg Q4W) achieved complete amyloid clearance status based on a threshold 24.1 Centiloid value. Most participants achieving amyloid clearance starting at 12 or 24 weeks remained amyloid negative for the duration of their florbetapir PET measurements.

Dose proportional increases were observed in both Cmax and exposure (AUC) following single and multiple doses. Single doses of 10, 20, and 40 mg/kg had measurable donanemab concentration for at least 56 days post-dose with elimination t1/2 of approximately 10 days. Multiple doses resulted in either no (10 mg/kg Q4W) or very limited exposure accumulation (10 mg/kg Q2W; 20 mg/kg Q4W). Quantifiable concentrations were detected in CSF samples collected from patients treated with single and multiple donanemab doses with CSF to serum concentration ratio of approximately 0.2% across all patients and dose levels.

Across all dose groups, there were no significant changes from baseline in any of the cognitive measures with donanemab treatment (data not shown).

5.4.2. Further published studies

Shcherbenin et al., 2022. Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes The TRAILBLAZER-ALZ Randomized Clinical Trial (the study also reported by Mintun et al., 2021)

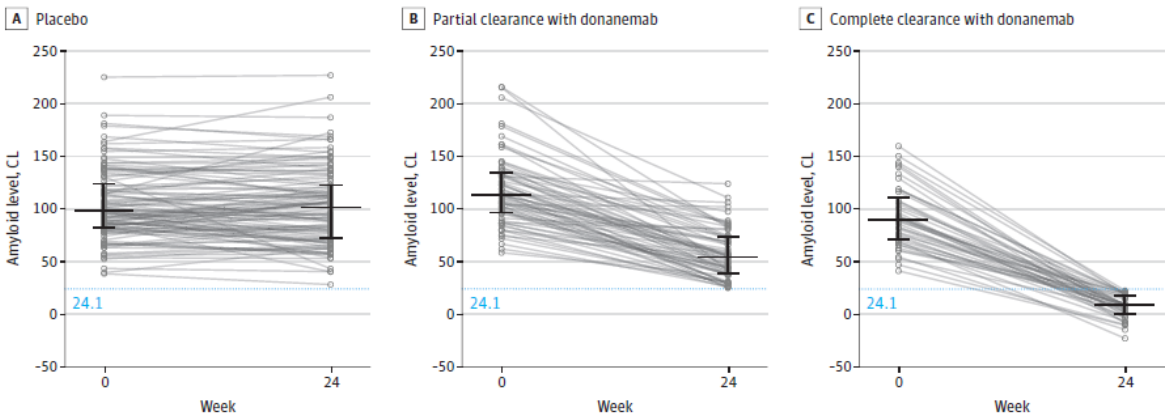
Please refer to Mintun et al., (section 5.4) for the study description.

In these exploratory post hoc analyses, the authors investigated donanemab-induced amyloid reduction and associations between amyloid lowering and tau PET. Participants were considered to achieve complete amyloid plaque clearance if post- treatment amyloid level was below an amyloid threshold of 24.1 CL, which is the same threshold required for amyloid levels consistent with a diagnosis of AD (Mintun et al., 2021, Navitsky et a., 2018). Thresholds of 11 and 24.1 CL are very close to ones found in the PET-autopsy study to detect moderate to frequent plaques and intermediate to high AD neuropathological changes, respectively (La Joie et al., 2019).

RESULTS

The primary study randomized 272 participants (mean [SD] age, 75.2 [5.5] years; 145 female participants [53.3%]). The trial excluded 1683 of 1955 individuals screened. The rate of donanemab-induced amyloid reduction at 24 weeks was moderately correlated with the amount of baseline amyloid (Spearman correlation coefficient r, −0.54; 95% CI, −0.66 to −0.39; P < .001).

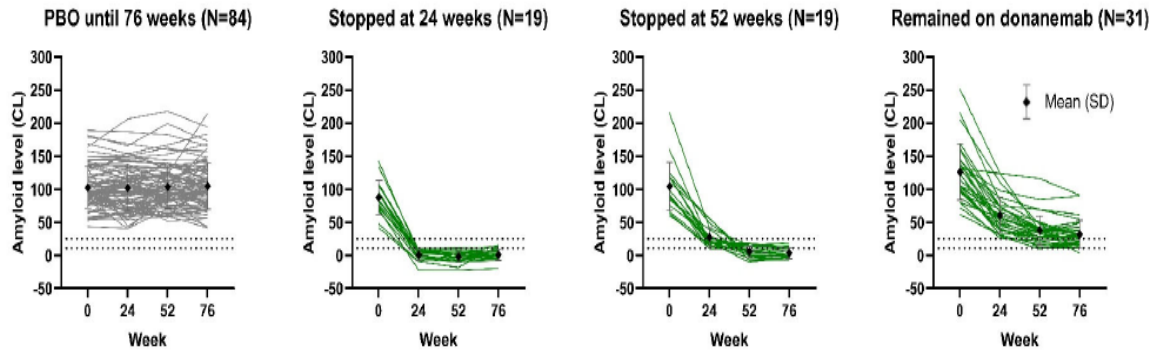
Figure 15. Association Between Amyloid Levels and the Magnitude of Amyloid Change at 24 Weeks



Median (IQR) amyloid levels (in centiloid [CL] units) at baseline and 24 weeks for participants receiving placebo (A), donanemab-treated participants with partial amyloid clearance at week 24 (B), and donanemab-treated participants with complete amyloid clearance at week 24 (C) demonstrating the change owing to donanemab treatment. Mean (SD) values along with partial vs complete amyloid clearance and treatment vs placebo comparisons can be found in eTable 2 in Supplement 2. Only participants with follow-up positron emission tomography scans are included.

Individual changes in florbetapir PET showed that the PET signal decreased on treatment with donanemab and did not increase again over prolonged period of time after discontinuation of the treatment (see the figure below).

Figure 16. Individual Participant Trajectories Showing Amyloid Levels Are Maintained Once Donanemab Treatment Is Discontinued



At 24 weeks, 19 participants were switched to placebo; at 52 weeks, 19 participants were switched to placebo, and 31 remained on donanemab until end of study. The 11 and 25 CL thresholds are indicated with dotted lines. The mean (black diamonds) and standard deviation (error bars) can also be found in eTable 2.

Notes: Only participants with interpretable amyloid scans taken at all timepoints were included in this dose-dependent subgroup analysis. Note, follow-up florbetapir scans were processed individually when the dose change decision was being made during the trial. The longitudinal trajectories presented in this manuscript and eFigure 3 were generated using longitudinal pipeline, where follow-up images were spatially normalized to the corresponding baseline scan before quantification.

CL = Centiloids

Modelling data suggest that amyloid would not reaccumulate to the 24.1-centiloid threshold for 3.9 years (95% prediction interval, 1.9-8.3 years) after discontinuing donanemab treatment. Donanemab slowed tau accumulation in a region-dependent manner as measured using neocortical and regional standardized uptake value ratios with cerebellar gray reference region. A disease-progression model found a significant association between percentage amyloid reduction and change on the integrated Alzheimer Disease Rating Scale only in apolipoprotein E (APOE) ε4 carriers (95% CI, 24%-59%; P < .001).

Brody et al. 2016: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Safety, Pharmacokinetics, and Biomarker Results of Subcutaneous Bapineuzumab in Patients with mild to moderate Alzheimer's disease

This randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase II study (NCT01254773) was conducted at 28 centers in United States from 16 December 2010 to 14 January 2013.

This study assessed the effects of monthly subcutaneous (SC) bapineuzumab versus placebo (12 injections in total) on cerebral amyloid signal in amyloid-positive patients with mild to moderate AD. The incidence of amyloid-related imaging abnormalities–edema/effusion (ARIA-E), pharmacokinetics, pharmacodynamics, immunogenicity, and other safety aspects of bapineuzumab were also evaluated. Randomization was balanced and was stratified by APOE*E4 allele status (carrier versus non-carrier). The patients were randomized (1 : 1 : 1 : 1) to SC bapineuzumab 2, 7, or 20 mg/month or placebo and received flortaucipir PET imaging at baseline, months 6 and 12, or at early termination (ET).

Primary endpoint: The primary endpoint was the change from baseline to month 12 in cerebral amyloid signal as measured by florbetapir PET scan, in a global cortical average (GCA) of 5 regions of interest (ROI), consisting of the anterior cingulate, frontal cortex, lateral temporal cortex, parietal cortex, and posterior cingulate/precuneus.

A PET scan time of 15 min duration was performed beginning 50 (±5) min after intravenous injection of 10±1 mCi (370 MBq) of 18F-florbetapir. An standardized uptake value ratios (SUVRs) for each ROI was calculated by dividing the standardized uptake value (SUV) of the target region by the SUV of cerebellar gray matter (reference region) per established methods by Johnson et al. (2013; Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. Alzheimers Dement 9, S72-S83).

Men and women, aged between 50 to 89 years (inclusive), diagnosed with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDSADRDA) criteria, were enrolled. Other major inclusion criteria were: florbetapir (18F-AV-45) PET scan demonstrating significant amyloid burden, as determined by visual analysis of the PET image by qualified readers at a single imaging core laboratory; brain magnetic resonance imaging (MRI) scan consistent with the diagnosis of AD; a Mini-Mental State Examination (MMSE) score of 18 to 26 (inclusive) at screening; a Rosen Modified Hachinski Ischemic score of 4 or less; and the availability of a responsible caregiver.

Results: A total of 146 patients (2 mg/month: n = 37; 7 mg/month: n = 36; 20 mg/month: n = 37; placebo: n = 36) were randomized and received at least 1 dose of the study medication. For the dosed patients, the demographic and baseline characteristics were generally balanced across the treatment groups, except for the 7 mg/month group, which had nominally higher ratings of disease severity on MMSE and ADAS-Cog. The majority of patients were women (57.5%), and white (97.3%). More than half of the patients (60.3%) were APOE*E4 carriers, most with 1 copy of the allele.

The florbetapir PET analysis population included 138 patients (2 mg/month: n = 35; 7 mg/month: n = 34; 20 mg/month: n = 36; placebo: n = 33).

At month 12, the LS mean change from baseline was in a negative direction in each bapineuzumab group (an indication of a reduction in fibrillar amyloid burden), compared with no change in the placebo group. A significant reduction from baseline to month 12 in SUVR was reported only for the 7 mg/month group (p = 0.038), but there were no significant between group differences for this measure and no evidence of dose-related trends. The MMRM analyses of SUVRs for individual ROIs (frontal cortex, anterior cingulate, lateral temporal cortex, parietal cortex, and posterior cingulate/precuneus) did not show significant changes from baseline at month 12 except for the 7 mg/month group for anterior cingulate (p = 0.033), parietal cortex (p = 0.048), and posterior cingulate/precuneus (p = 0.024) ROIs. No between group differences were noted.

In subgroup analyses based on disease severity, change in SUVR from baseline to month 12 was significant only in the 7 mg/month group in patients with mild AD (p = 0.016). Similarly, in the subgroup analysis based on APOE*E4 status, the baseline to month 12 change was significant only for non-carriers (p = 0.049) in the 7 mg/month group. The only between-group difference that was statistically significant was for 7 mg/month versus placebo in patients with mild AD (p = 0.046).

Trough serum bapineuzumab concentrations increased with increasing bapineuzumab dose in an approximately dose-proportional manner. Mean CSF bapineuzumab concentrations at month 12 or ET were 0.75, 1.92, and 5.37 ng/mL for the 2, 7, and 20 mg/month dose groups, respectively. A dose-dependent increase in plasma Aβ concentrations was observed in bapineuzumab groups at month 12 (data not shown). Plasma Aβ concentrations in the placebo group were consistent at baseline and month 12.

Swanson et al. 2021. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aß protofibril antibody

This was a randomized double-blind clinical trial, that utilized a Bayesian design with response-adaptive randomization to assess 3 doses across 2 regimens of lecanemab versus placebo in early Alzheimer's disease, mild cognitive impairment due to Alzheimer's disease (AD) and mild AD dementia.

The study aimed to establish the effective dose 90% (ED90. The primary endpoint was Bayesian analysis of 12-month clinical change on the Alzheimer's Disease Composite Score (ADCOMS) for the ED90 dose. Key secondary endpoints included 18-month Bayesian and frequentist analyses of brain amyloid reduction using positron emission tomography; clinical decline on ADCOMS, Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14); changes in CSF core biomarkers; and total hippocampal volume (HV) using volumetric magnetic resonance imaging.

Results: A total of 854 randomized subjects were treated (lecanemab, 609; placebo, 245). At 12 months, the 10-mg/ kg biweekly ED90 dose showed a 64% probability to be better than placebo by 25% on ADCOMS. At 18 months, 10-mg/kg biweekly lecanemab reduced brain amyloid (-0.306 SUVr units) while showing a drug-placebo difference in favour of active treatment by 27% and 30% on ADCOMS, 56% and 47% on ADAS-Cog14, and 33% and 26% on CDR-SB versus placebo according to Bayesian and frequentist analyses, respectively. CSF biomarkers were supportive of a treatment effect.

Klein et al., 2019. Gantenerumab reduces **amyloid-β** plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis

A subset of patients from previous two studies who subsequently entered the open-label extensions (OLEs) were included in this substudy. Patients aged 50 to 90 years with a clinical diagnosis of probable prodromal to moderate AD were assigned to 1 of 5 titration schedules (ranging from 2 to 10 months) with a target gantenerumab dose of 1200 mg every 4 weeks. The main endpoint of this substudy was change in amyloid- β plaque burden from OLE baseline to week 52 and week 104, assessed using florbetapir PET. Florbetapir global cortical signal was calculated using a prespecified SUVR converted to the Centiloid scale.

Results: Sixty-seven of the 89 patients initially enrolled had ≥ 1 follow-up scan by August 15, 2018. Mean amyloid levels were reduced by 39 Centiloids by the first year and 59 Centiloids by year 2, a 3.5-times greater reduction than was seen after 2 years at 225 mg in one of the previous studies (SR). At years 1 and 2, 37% and 51% of patients, respectively, had amyloid-β plaque levels below the amyloid-β positivity threshold.

Florbetapir uptake reduction was seen in all brain regions known to be involved with amyloid pathology. Highest unadjusted reductions were observed in the cingulate, frontal, and striatum areas. When adjusted for baseline amyloid burden, the caudate region showed the greatest regional reduction.

5.4.3. Published studies evaluating various methodologies for quantitative measurements of florbetapir PET

Salloway et al. 2018. Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to- moderate Alzheimer's disease (BLAZE)

This double-blind, placebo-controlled, randomized phase II study enrolled patients with mild-to-moderate AD and a Mini-Mental State Examination (MMSE) score of 18–26. In part 1 of the study,

patients were 2:1 randomized to receive low-dose subcutaneous (SC) 300 mg crenezumab every 2 weeks (q2w) or placebo for 68 weeks; in part 2, patients were 2:1 randomized to receive high-dose intravenous (IV) 15 mg/kg crenezumab every 4 weeks (q4w) or placebo for 68 weeks. The primary endpoint was change in amyloid burden from baseline to week 69 assessed by florbetapir positron emission tomography (PET) in the modified intent-to-treat population. Secondary endpoints were change from baseline to week 69 in cerebrospinal fluid (CSF) biomarkers and fluorodeoxyglucose PET, and change from baseline to week 73 in 12-point Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog12) and Clinical Dementia Rating Sum of Boxes (CDR-SB).

Florbetapir PET scans were performed at screening (baseline) and week 47 and week 69 visits, or at ET/D if necessary.

Two independent, blinded processing pipelines were used to measure composite cortical SUVR values for each scan. The SUVR is the ratio of the mean standard uptake value (SUV) of the composite neocortical region to the SUV of a reference region (as described below).

The first pipeline, developed and executed by Molecular NeuroImaging (MNI; Molecular NeuroImaging LLC, New Haven, CT), was used for the predefined primary analysis and the post-hoc exploratory analysis. Baseline PET images were registered to the baseline T1 MRI. The transformation matrix derived from normalizing the MRI to standard space, TMRI, was applied to the PET images. Follow-up PET images were registered to the baseline MRI and then normalized by applying TMRI. Mean SUVs were extracted from regions of interest (ROIs) using an anatomical template that was individually refined by the gray matter mask segmented from the baseline MRI. The composite cortical ROI included the frontal cortex, parietal cortex, lateral temporal cortex, and posterior cingulate cortex (PCC). Two reference ROIs were used to calculate SUVR: 1) the cerebellar cortex, which was the predefined ROI for the primary outcome (SUVRCB); and 2) anterior bilateral volumes of subcortical white matter, which was measured as part of the initial analysis but only used for the post-hoc exploratory measurements (SUVRMNI-WM).

The second pipeline, a PET-only procedure developed and executed by Banner Alzheimer's Institute (BAI; Phoenix, AZ) and recommended by Avid Radiopharmaceuticals (Philadelphia, PA) was used only for post-hoc exploratory analysis (Chen et al., 2015). Baseline PET images were registered directly to a standard florbetapir PET template, which was also used to extract SUV measurements from anatomically defined ROIs. The transformation matrix, TPET, was saved. Follow-up PET images were registered to the baseline PET and then normalized by applying TPET. The composite cortical ROI included the inferior medial frontal gyrus, superior parietal cortex, lateral temporal cortex, PCC, anterior cingulate cortex, and precuneus. The reference ROI was composed of white matter and included corpus callosum and centrum semiovale (SUVRBAI-WM).

Results: 91 patients were enrolled and randomized (low-dose SC cohort: crenezumab (n = 26) or placebo (n = 13); high-dose IV cohort: crenezumab (n = 36) or placebo (n = 16)).

The primary endpoint was not met using a prespecified cerebellar reference region to calculate standard uptake value ratios (SUVRs) from florbetapir PET. Exploratory analyses using subcortical white matter reference regions showed nonsignificant trends toward slower accumulation of plaque amyloid in the high-dose IV cohort. Plots comparing SUVR at baseline versus week 69 for individual patients indicated greater than expected longitudinal variability using the cerebellar reference region, including many placebo patients with apparent lowering in florbetapir SUVRs at week 69 (Additional file 2: Figure S1A, D). Using the exploratory analyses with white matter reference regions (SUVRBAI-WM and SUVRMNI-WM), the longitudinal variability observed in the primary analysis was reduced, and fewer placebo patients showed evidence of amyloid reduction (Additional file 2: Figure S1B, C, E, F).

Figure 17. Changes on florbetapir PET as evaluated by means of 3 methods for SUVR calculation: cerebellar gray MNI-CB (a,d), BAI-WM (b,e), and MNI-WM (c,f).

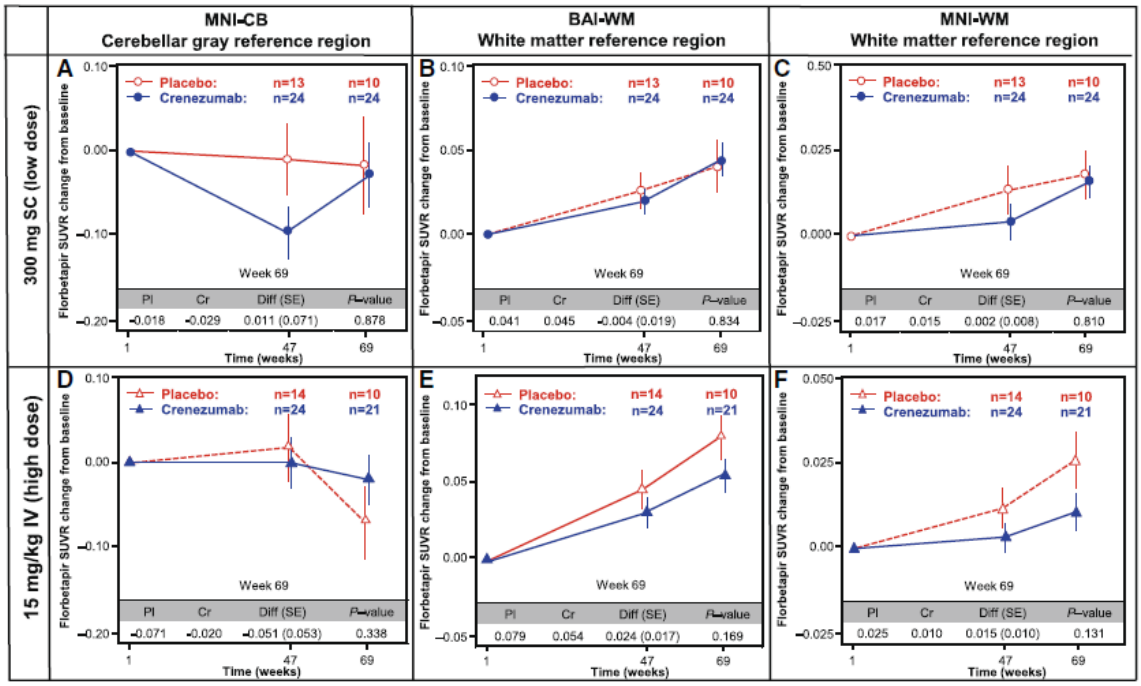


Fig. 2 Amyloid PET analysis. Analysis of the florbetapir change from baseline using three different methods for the calculation of SUVR: in the cerebellar gray MNI-CB (**a,d**), BAI-WM (**b,e**), and MNI-WM (**c,f**). The primary difference between these methods is the choice of reference region: cerebellar gray matter ($SUVR_{MNI-CB}$) or subcortical white matter ($SUVR_{MNI-WM}$ and $SUVR_{BAI-WM}$). The reference regions in both the low-dose SC (**a–c**) and high-dose IV (**d–f**) cohorts are shown. *BAI* Banner Alzheimer's Institute, *BL* baseline, *Cr* crenezumab, *Diff* difference, *IV* intravenous, *MNI* molecular neuroimaging, *Pl* placebo, *SC* subcutaneous, *SE* standard error, *SUVR* standard uptake value ratio, *WM* white matter, *CB* cerebellar

In both cohorts, a significant mean increase from baseline in CSF Aβ(1–42) levels versus placebo was observed, but the sample is very small (10 vs 20 patients and 8 vs 17 patients on placebo and verum in the low and high-dose cohorts, respectively).

Nonsignificant trends toward ADAS-Cog12 and CDR- SB benefits were identified in a mild (MMSE 20–26) subset of the high-dose IV cohort.

Fleisher et al. 2017: Use of white matter reference regions for detection of change in florbetapir positron emission tomography from completed phase 3 solanezumab trials

This was a post hoc retrospective analysis of a sub-set of patients with mild dementia due to AD from 2 multinational, randomized, double-blind, placebo-controlled studies of solanezumab 400 mg (EXPEDITION and EXPEDITION2; ClinicalTrials.gov numbers: NCT00905372 and NCT00904683).

The aim of this analysis was comparison of the subject-specific white matter (SSWM) and whole cerebellum (CBL) reference regions for power to detect longitudinal change in amyloid positron emission tomography signal.

Methods: Positive florbetapir PET scans were analyzed from participants (66 placebo treated and 63 solanezumab treated). For comparison to CBL, a second normalization was performed on longitudinal data using an SSWM correction factor (SSWM normalization ratio [SSWMnr]). Analysis of covariance assessed baseline to 18-month change between treatment with solanezumab and placebo. Sample and effect size estimations provided magnitude of observed treatment changes.

Results: Longitudinal percent change between placebo and solanezumab using CBL was not significant (P = 0.536) but was significant for SSWMnr (P = 0.042). Compared with CBL, SSWMnr technique increased the power to detect a treatment difference, more than tripling the effect size and reducing the sample size requirements by 85% to 90%.

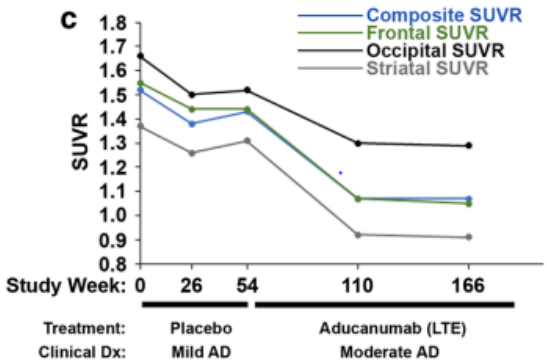
The Authors' conclusion: Adjusting longitudinal standardized uptake value ratios with an SSWM reference region in these anti-amyloid treatment trials increased mean change detection and decreased variance resulting in the substantial improvement in statistical power to detect change.

5.4.4. Validation of Florbetapir PET findings on treatment vs. autopsy

No study has been conducted where autopsy data in the patients treated with ATTs would be evaluated. The following publications were submitted.

Honig et al., 2022 (Abstract) describes an autopsy case of a patient with AD treated with lecanemab over 6 years. Clinically, memory symptoms started at age~77. Study entry was at age~80, with mild dementia, CDR 0.5, CDR-SB 3, and MMSE 24. Florbetapir PET scan was positive at baseline, and negative after 53 weeks DB treatment and at start of OLE. No ARIA developed. In autopsy the pattern of significant tau pathology accompanied by only a mild degree of β amyloid deposits, (A1B3C2), was detected, which is uncommon in typical (untreated) Alzheimer's disease (In the NACC neuropathology dataset, only 2% of brains with Braak B2 or B3 show Thal stage A0 or A1). The Authors conclude that this pattern suggests that lecanemab treatment resulted in a reduction in brain amyloid, consistent with the amyloid PET scanning results in this patient.

Plowey et al., 2022 describes an 84-year-old woman who was randomized to the placebo arm of the PRIME Phase 1b study (221AD103). The patient progressed to moderate dementia (MMSE=14/30), beyond the targeted early AD treatment stage, before receiving aducanumab in the long-term extension (LTE). The patient then received 32 monthly doses of aducanumab. At screening and during the placebo-controlled period of PRIME, during which the Patient was randomized to placebo, Amyloid PET SUVRs ranged from 1.5 to 1.7 in cortical regions and registered 1.4 in the striatum, consistent with at least a Thal Phase 3 of Aβ plaque deposition. On aducanumab, SUVRs to dropped to<1.1 in these regions in the first 54 weeks of the LTE.



MRI examinations were negative for amyloid-related imaging abnormalities (ARIA). The post-mortem neuropathologic examination showed sparse residual Aβ plaque engaged by amoeboid reactive microglia and tau-related neocortical neurofibrillary degeneration (Braak stage V, NIA/AA Stage B3).

VandeVrede et al., 2023 describes 2 patients who were autopsied after treatment with aducanumab. The publication does not contribute substantial data on amyloid PET.

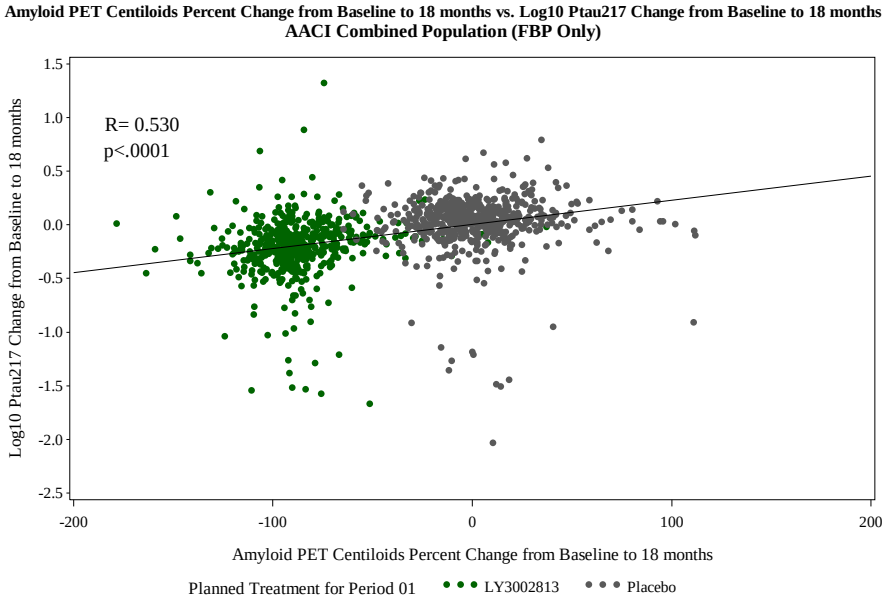
5.4.5. Validation of Florbetapir PET against amyloid and/or tau biomarkers, or clinical diagnostic parameters

There is an extensive literature showing a relationship between fluid (CSF and plasma) biomarkers and amyloid PET in patients coming for diagnosis (Iaccarino et al. 2023).

CSF and plasma Aβ were not evaluated in donanemab Phase 3 Study AACI. In the donanemab Phase 2 Study I5T-MC-AACG (AACG), the significant decrease in florbetapir PET SUVr in the donanemab treatment group was accompanied by a modest, albeit somewhat variable, increase in plasma Aβ42/40 ratio (Pontecorvo et al. 2022). It has also been reported that an increase in CSF and plasma Aβ42/40 ratio accompanies reduction in florbetapir PET SUVr after treatment with lecanemab (van Dyck et al. 2023).

It is widely postulated that phosphorylation of tau may be downstream of aggregated Aβ deposition in the natural history of disease, thus it may be more reasonable to expect fluid markers of phosphorylated tau to change in the same direction as amyloid PET markers after treatment with an ATT. In the donanemab Study AACI, there was a correlation between quantitative (CL) change from baseline in florbetapir PET and change from baseline in plasma P-tau217 at each PET time point of 6, 12, and 18 months (see the figure).

Figure 18. Amyloid PET Centiloids percent change from baseline AACI combined population (florbetapir only).



Note: Spearman's rank used for correlation coefficient
Source data: \prd\ly3002813\i5t_mc_aaci\intrm7\data\analysis\restricted
Source program: \prd\ly3002813\i5t_mc_aaci\intrm7\programs\tfl\primary\cor_ptau217chg_amy_pctchg.sas
Source output: prd\ly3002813\i5t_mc_aaci\intrm7\output\restricted\tfl\cor_ptau217chg_amy_pctchg.rtf

In the donanemab Study AACI, correlations between a greater amyloid PET reduction (CL) and P-tau217 reduction with less clinical progression (assessed by changes in iADRS and CDR-SB) were not observed within either treatment group separately (for example, within the donanemab treatment group and within placebo).

5.4.6. Possible factors influencing florbetapir uptake/binding during treatment with AATs, test-re-test reliability and inter- and intra-reader agreement

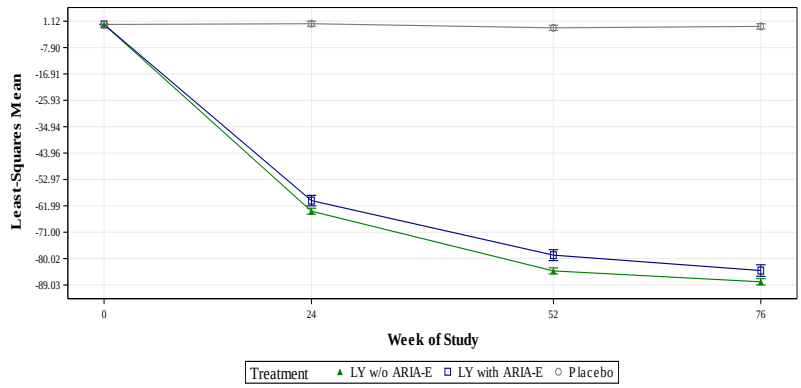
An anti-Aβ-antibody (Crenezumab; Roche) and 4 γ-secretase inhibitors (L-685458, S1288, Compound W, and DAPT) were tested for drug-drug interactions at the Florbetapir binding site and the results were previously submitted in the Amyvid marketing authorisation application (Report TR-AV-45-081; Module 4.2.1.4). No risk for drug-drug interactions at the florbetapir-binding site was detected.

In a non-clinical study (report submitted with the responses to the first RSI) binding of 18F-florbetapir to Alzheimer's Disease (AD) frontal cortex (FC) gray matter brain tissue homogenates was evaluated in the presence of varying concentrations of the antibodies donanemab and lecanemab. Across the concentration range evaluated (0.032 nM to 1000 nM), donanemab showed weak inhibition of 18F-florbetapir, though inhibition was observed at the top two concentrations tested (0.32 µM and 1 µM donanemab). The IC50 for donanemab was extrapolated to be greater than or equal to 1 µM. Lecanemab showed weak to no inhibition of 18F-florbetapir; an IC50 could not be extrapolated.

Data from the donanemab programme indicate that re-accumulation rates for patients who stopped donanemab treatment were consistent with the rates of accumulation in natural history studies (Shcherbinin et al. 2023 and own data from donanemab study – response document).

Data from the donanemab Study AACI demonstrate that, at difference with amyloid PET, tau PET signal is not reduced in patients treated with ATTs, with rather some marginal evidence for slowing of tau accumulation in subsets of patients (Sims at al. 2023). Additionally, within the donanemab programme, sensitivity analyses based on ARIA indicated that there was no material difference between the level of amyloid clearance observed, regardless of whether patients experiencing ARIA over the course of the trial were included or excluded from the analysis. A greater reduction in amyloid was observed in patients who did not experience ARIA.

Figure 19. Plot of Florbetapir Centiloid Longitudinal Avid Analysis - Change from Baseline (LS-Mean Estimates from MMRM Model; evaluable efficacy set, Study I5T-MC-AACI (Primary Outcome Database Lock))



Test-re-test reliability and inter-/intra-reader agreement has not been evaluated. The Applicant is of the opinion that diagnostic efficacy of the test will be similar in diagnosing presence of beta-amyloid in the brain with or without treatment.

5.4.7. Discussion on clinical efficacy

The Applicant seeks approval of Amyvid in monitoring of treatment effects on the brain amyloid in the patients with AD. Concretely, the proposed indication wording is “Imaging of β amyloid neuritic plaque density in the brains of adult patients receiving amyloid-targeting therapy.”

It is agreed that amyloid PET products are being increasingly used in the monitoring of treatment efficacy and it is expected that with the first approval of disease-modifying products medical need in the adequately tested and well-characterised diagnostic tools, reliably monitoring treatment effects, will arise. Consequently, submission of this variation procedure to gain approval in new indication is generally welcome.

Of note, initially no clinical data relevant for the new indication claim have been submitted and the assessment referred to the data package submitted with the previous type II variation (EMEA/H/C/002422/II/0044), that contains only published literature. With the responses to the first RSI additional data including those from own studies with donanemab have been provided.

Key publications mentioned by the Applicant seem to be Sims et al. 2023, Mintun et al. 2021, Budd Haeberlein et al. 2022, and Van Dyck et al. 2023. All four publications describe studies in which amyloid-targeting treatment was applied against placebo in patients with early AD. All studies tested efficacy utilising clinical parameters, but amyloid PET was also used to track changes in the amyloid load in the brain.

In the study described by Sims et al., 2023 and Mintun et al., 2021, florbetapir PET showed pronounced decrease in uptake of florbetapir on donanemab, but not on placebo. Differentiation between donanemab and placebo in clinical parameters and other biomarkers was not similarly pronounced and some changes (e.g., tau PET, MRI) showed inconsistent results. Other methods of measuring amyloid have not been reported (or were not applied in the study). Therefore, no clear supportive evidence can be derived from these studies.

Budd Haeberlein et al., 2022 publication describes a post hoc evaluation conducted based on the pre-planned analysis of two phase III studies with aducanumab stopped prematurely. The studies included various biomarkers to estimate changes in the patients' condition and as a supportive information for assessment of efficacy. Within the context of this variation the correlation analyses conducted across the biomarkers and between these biomarkers and clinical parameters are of interest. Florbetapir PET showed dose-dependent reduction in the PET signal on treatment with aducanumab. However, correlation analysis of florbetapir PET against clinical parameters did not show consistent results. Florbetapir PET signal correlated with the plasma levels of phosphorylated tau-181, which may be suggestive of downstream effects of amyloid clearance on burden of tau in the brain. Correlation analysis between the changes in florbetapir PET and in the amyloid (CSF, plasma) was not conducted (or not presented). Such analysis would have been of interest.

The following key limitations have been noticed: E.g., the biomarker analyses were conducted in the subpopulations of various sizes (e.g., florbetapir PET substudies included 488 and 585 patients and CSF was collected in 78 and 53 patients in EMERGE and ENGAGE studies respectively, whereas longitudinal tau PET imaging was performed in 37 patients in both studies, correlation analyses for tau PET and p-tau181 against clinical parameters included 182-240 and 514-581 patients respectively depending on the study) so that comparisons across parameters are difficult; Data might have been impacted by drop-outs (or missing data); Some of the applied methodologies/biomarkers and thresholds used for patient selection and assessment of treatment effects were experimental, or their validity is uncertain (e.g., centiloid metrics, Tau PET, measurements of tau and amyloid, thresholds applied for PET). This complicates interpretation of the data; Retrospective character of the analyses limits the scientific value of the data.

In conclusion, the publication provides some interesting data on correlation analyses, which could be regarded as supportive to some extent, but the mentioned limitations create high uncertainty. Most importantly, absence of correlation analysis between Florbetapir PET and actual amyloid measurements is a relevant limitation.

Van Dyck et al., 2023 described a study evaluating efficacy of lecanemab against placebo in patients with early AD. Amyloid PET showed clear differentiation between the treatment arms with assumed improvement on lecanemab that became obvious at 3 months and further increased towards end of treatment. The Authors state that effects were seen also on other biomarkers. However, no data have been reported in the publication.

Notably, the study utilised different types of amyloid tracers for PET imaging and the publication does not present data with florbetapir PET separately. It is unclear to which extent the observed changes on the PET can be generalised across various tracers and concretely, to florbetapir. Validity of centiloid units across various tracers and in the setting of longitudinal assessments has not been discussed. Similarly to the study by Mintun et al., correlation analysis against other diagnostic tests measuring amyloid and response to treatment has not been presented.

Lowe et al., 2021: This was a small Phase 1b study that primarily aimed at testing lower doses and different dosing regimens of donanemab in the patients with MCI or mild to moderate AD. Florbetapir PET was utilised as a PD parameter to monitor the changes in the beta amyloid density in the brain.

Overall, the study data showed that uptake of florbetapir in the brain decreased in a dose-dependent manner when evaluated by means of Centiloid. Dose-dependent increase in systemic and CSF donanemab concentration was also reported. In combination with the dose-dependent changes on the florbetapir PET, this may suggest a potential relationship between the administered donanemab and the changes on the PET. However, the absence of correlation analysis and small size of the study are limiting factors in data interpretation. Limitations, such as unknown or unavailable validation of the methodologies also apply to this study.

Further published evidence suggests that reduction in amyloid burden as measured by means of Florbetapir PET takes place in relevant brain regions associated with AD-related amyloid accumulation (Klein et al.), that reduction in amyloid burden may have positive effects on tau aggregation in the brain (Shcherbenin et al.), and may be consistent with changes in clinical symptoms (Swanson et al.). However, also discrepant findings between florbetapir PET and Aβ concentrations in plasma have been observed (Brody et al.).

Further published evidence presented by the Applicant has not been described due to relevant deficiencies, or difficulties in data interpretation. E.g., a disclosure by Barkhof et al. (2023) has been mentioned, which is a power point presentation of study results and is not acceptable as published evidence. The publications by van Dyck et al., Honig et al. (2018), Salloway et al.(2021), do not include concrete data on florbetapir PET and Bateman et al. is a review article that does not provide any evidence.

Universal reference of truth for diagnostic agents is histology analysis. However, such analysis is not feasible to track longitudinal changes in AD. Two case reports presented (Honig et al., 2022 and Plowey et al., 2022) described autopsy cases of the patients (one in each publication) treated with lecanemab and aducanumab, who had improved amyloid PET (Florbetapir PET in both cases) shortly before death. Both patients had low amyloid load combined with pronounced/progressed stage of tau neurofibrillary aggregation. In autopsy the pattern of significant tau pathology accompanied by only a mild degree of β amyloid deposits was detected, which is uncommon in typical (untreated) Alzheimer's disease (In the NACC neuropathology dataset, only 2% of brains with Braak B2 or B3 show Thal stage A0 or A1). This pattern suggests that the received treatment resulted in a reduction in brain amyloid, consistent with the amyloid PET scanning results in the respective patient. This information is limited but reassuring.

The submitted data on correlation analyses between Florbetapir PET and other amyloid biomarkers, clinical parameters of AD, donanemab concentrations, do not provide sufficient evidence to support the validation of Florbetapir PET longitudinal changes for monitoring of ATT treatment. It must be noted that PET scans reflect the cumulative deposition or removal of aggregated protein over time, whereas fluid markers reflect the ongoing turnover of proteins at any given point in time. Therefore, it is not necessarily the case that fluid markers should change in the same degree or direction as amyloid PET markers after treatment with ATT. Also, clinical parameters do not seem to show similar degree of

changes as amyloid PET, which may be explained by the fact that patients with AD often have concomitant confounding conditions (other types of dementias, tauopathies, vascular pathology, etc.) which could lead to smaller effect size on clinical parameters compared to the degree of PET signal changes. Other confounding/interfering factors (e.g., delayed clinical response) may also be involved.

To summarise, evidence submitted by the Applicant suggests that florbetapir PET may be suitable for monitoring of treatment effects with regard to beta-amyloid clearance. This assumption is largely based on the fact that in the majority of the studies uptake of florbetapir was decreased on amyloid-targeted treatment, but did not change or was slightly increased on placebo suggesting clear differentiation. It is agreed that submitted publications show substantial consistency in this regard. However, the evidence is burdened by a number of limitations and uncertainties, such as absence of information on exact methodology for interpretation of Florbetapir PET images (blinding, number of reviewers, qualification of the reviewers, etc.), or use of sub-standard or experimental methodologies for image interpretation, small size of some of the studies/exploratory character (e.g., retrospective analyses), partly discrepant findings in terms of PET correlation against other parameters of AD, and, most importantly, lack of a well-defined and reliable standard reference that could indirectly indicate true changes in brain amyloid burden (it is acknowledged that direct measurement of amyloid in the brain would not be feasible). Additional information submitted with the responses to the first RSI has not provide substantial additional evidence in the sense that changes in florbetapir PET could not be validated against other clinical parameters in the patients with AD.

However, the ability of florbetapir PET to detect the absence or presence of beta-amyloid in the brain (sensitivity, specificity) with adequate accuracy has been established at the time of the MAA of Amyvid. Also, correlation between the PET signal and the actual amount of amyloid in the brain (on autopsy) was proven at the time of the initial MAA. Consequently, it may be assumed that diagnostic efficacy (sensitivity and specificity, accuracy of the test, correlation of the PET signal vs. actual amyloid load in the brain) of Amyvid PET may be extrapolated from the approved clinical setting (support in the initial diagnosis of AD) to the new clinical use (monitoring of treatment effects on the brain amyloid), provided that:

1. Amyvid PET is to provide the same diagnostic information as already approved (i.e., binary answer/inform on presence, or absence of beta-amyloid in the brain),
2. The same image reading methodology is applied as recommended in the SmPC (i.e., visual read supported in some cases with quantitative measurements), and
3. There is a reasonably high certainty that efficacy of Amyvid PET is not affected by amyloid-targeting treatment, or, in other words, it can be convincingly demonstrated that the observed changes on the PET can be ascribed to actual changes in amyloid burden.

The Applicant argues that effects such as competitive binding at the same site, pathophysiological processes, structural changes, changes in the site perfusion/Florbetapir distribution do not represent the reason for observed changes on florbetapi PET on ATTs based on the following factors:

- Data from the donanemab programme indicate that re-accumulation rates for patients who stopped donanemab treatment were consistent with the rates of accumulation in natural history studies (Shcherbinin et al. 2023). Also, individual re-accumulation in patients achieving amyloid clearance at 24 or 52 weeks (many of whom met stopping criteria and ceased treatment at that time) on donanemab is significantly below the baseline amyloid level over the following 6 to 12 months. In the case of competitive binding, cessation of ATT treatment would have led to a quick increase in Florbetapir PET signal.

- In case possible pathophysiological processes, such as perfusion changes or ARIA or other AE, impacted amyloid PET signal, it would be expected that similar effects would be observed with tau-PET signal as well. Data from the donanemab Study AACI show that, in contrast with amyloid PET, tau PET signal is not reduced in patients treated with ATTs, with rather some marginal evidence for slowing of tau accumulation in subsets of patients (Sims et al. 2023).
- Within the donanemab programme, sensitivity analyses based on ARIA indicated that there was no material difference between the level of amyloid clearance observed, regardless of whether patients experiencing ARIA over the course of the trial were included or excluded from the analysis.

The data presented indeed suggest that the changes observed on Florbetapir PET may not be explained with drug-drug interactions, physiological or structural changes in the brain. However, the key relevant limitation of these arguments is that partly no data were presented (e.g., to support the claim that no specific effects, off-target uptake, etc. were reported in the studies), or if data have been presented the methodology of image evaluations is unclear, and most importantly, only group-level data are being evaluated. Thus, the actual data on image analyses, image readings is unavailable and the arguments remain theoretical. The question of possible confounders which may influence Florbetapir PET after treatment with ATTs remains uncertain.

The Applicant claims that diagnostic efficacy (performance, accuracy) of Florbetapir can be extrapolated from the “diagnostic” approved indication to the new “monitoring” indication, since the same image interpretation procedures will be used in the new indication and as similar proportion of borderline amyloid accumulation cases is expected in the new indication compared to the approved one (i.e., frequency of the mistakes in the image read should be the same). This argumentation seems plausible.

However, it is apparent that in the clinical practice interpretation of the amyloid PET images will not be restricted to visual read criteria. Obviously, quantitative measurements of PET signal and their changes are being intensively used and the proposed image read criteria do not reflect current clinical practice. Publications by Plowey et al., Shcherbenin et al. and Lowe et al., clearly show that considerable fluctuation in the quantitative measurements of Florbetapir PET signal were observed on repeated assessments. No explanation has been provided, but these might have been due to the variability of tracer uptake, and/or variability in SUVR measurement procedures, etc. These data indicate the necessity and relevance of proper test-re-test variability assessment and of definition of a minimally relevant change in the tracer uptake that would differentiate true changes in the amyloid burden vs. standard test-re-test variability and intra-/inter-reader variability. The question of possible confounders which may influence Florbetapir PET after treatment with ATTs has also been addressed insufficiently.

Further, published literature reports increased variability of Florbetapir/amyloid PET signal in the longitudinal setting (compared to cross sectional) and various quantitative measurement methods may result in variable outcomes. As an example, Salloway et al., 2018 and Fleisher et al. evaluating various methodologies for Florbetapir PET interpretation (quantitative measurements) found that depending on the chosen reference region and methodology of measuring florbetapir uptake longitudinal measurement results may differ greatly. Additionally, study by Salloway et al., that tested 3 methodologies for measurement of longitudinal changes in the florbetapir PET in the patients treated with crenezumab and placebo showed that SUVRs measured on treatment using cerebellum as a reference region were highly variable and showed decrease in amyloid on placebo in some patients. Smaller variability was observed when SUVRs were measured utilising white matter as a reference region. This emphasizes the relevance of the chosen image interpretation methodologies to be used for evaluation of changes in florbetapir PET. Higher susceptibility of longitudinal evaluation of amyloid PET

measurements to variance compared to cross-sectional analyses has also been described by Landau et al., 2015 and Chen et al., 2015 (Landau SM, Fero A, Baker SL, Koeppe R, Mintun M, Chen K, et al. Measurement of longitudinal beta-amyloid change with 18F-florbetapir PET and standardized uptake value ratios. J Nucl Med 2015; 56:567–74.; Chen K, Roontiva A, Thiyyagura P, LeeW, Liu X, Ayutyanont N, et al. Improved power for characterizing longitudinal amyloid-beta PET changes and evaluating amyloid-modifying treatments with a cerebral white matter reference region. J Nucl Med 2015;56:560–6.).

The recommended visual read criteria for monitoring of treatment effects on the brain amyloid with Florbetapir do not reflect state of the art and extrapolation of diagnostic efficacy of Florbetapir from "diagnostic" setting to the new indication needs further substantiation. Therefore, A properly designed (fully blinded, several trained central readers, please refer to the relevant guidelines) reader study to evaluate test-re-test variability/reliability and technical performance of Florbetapir PET on repeated scans, including on ATT should be conducted. Images available from the AAT therapeutic studies (baseline and on treatment, placebo and verum, preferably various ATTs as available) and any other previous studies with repeated scans of Florbetapir can be utilised. The following should be evaluated:

a) Test-re-test variability (repeated scans to be used; measured in SUVRs and centiloids)

b) NI of an intra- and inter-reader variability of Florbetapir PET on ATT to the same parameters before start of ATT and comparison to placebo (within-patient comparison; two methods of image interpretation to be used: visual read as recommended in the SmPC currently and quantitative measurements: SUVRs and centiloids).

c) Based on the measured variabilities a threshold for minimally relevant change in Florbetapir PET signal (measured in SUVRs and centiloids) should be defined.

A proper image interpretation procedure, including quantitative measurement method (relevant reference region, thresholds, minimum relevant change definition, measurement units, etc.) should be developed and reflected in the SmPC. (MO)

Generalisability of the submitted evidence to all AATs has not been discussed properly. Majority of the relevant data supporting the indication claim derive from own donanemab trials. Evidence of diagnostic efficacy of Florbetapir during use in other ATT studies remains mostly limited to the active vs. placebo arm comparisons (without additional validation against other efficacy parameters/standard of truth). The difficulty of extrapolation across various ATTs is acknowledged and the broad indication claimed may be agreed. However, limitation of the submitted data (experience limited to the AA antibodies, e.g., donanemab) should be mentioned in the SmPC (section 4.4)(OC).

The Applicant has not provided concrete data on the impact on patient management or diagnostic confidence for Florbetapir. However, it is acknowledged that in the absence of approved amyloid targeted treatment, collection of such data may be challenging.

In any case, it is apparent that amyloid PET is being actively used in monitoring of AAT effects as a PD parameter. If approved, Florbetapir PET may be utilised for decision-making on treatment discontinuation.

5.4.8. Conclusions on the clinical efficacy

Efficacy data presented are insufficient to substantiate the claimed new indication. Additional data should be submitted. MO/OCs

5.5. Clinical safety and adaptation made to section 4.8 of the SmPC

Safety of the product in the new indication has not been discussed.

5.5.1. Proposed change to section 4.8

The following adaptation has been proposed (the deleted text is crossed, new text is displayed in bold) in the Section 4.8 of the SmPC:

"The safety profile of Amyvid is based on its administrations to ~~2,105~~ 5 847 subjects in clinical trials."

The total cumulative exposure is approximately 47 852 subjects. The cumulative number of subjects who were exposed to florbetapir in ongoing and completed clinical trials sponsored by Avid is 6223. It is estimated that approximately 27 757 subjects have been exposed to florbetapir in clinical trials sponsored by Lilly. Approximately 13 872 subjects have been exposed to florbetapir in trials sponsored by third-party pharmaceutical companies and investigator-initiated trials. Many of these studies are therapeutic trials in which florbetapir was used to image amyloid as a biomarker.

The florbetapir developmental clinical trial safety database used for ADR determination comprises 5847 subjects receiving 1 or more doses of florbetapir in 28 pivotal clinical trials of the florbetapir clinical development programme. This value is cited in the SmPC and RMP to provide proper context to the discussion of undesirable effects.

The most recent florbetapir PSUR provided to the European Medicines Agency was PSUR PBRER 13 (reporting period 07 April 2019 to 06 April 2022) in keeping with the current report submission schedule. In addition, florbetapir safety data were reviewed for PSUR PBRER 14 (reporting period 07 April 2022 to 06 April 2023), which was not distributed to the EU. No new, significant safety information was identified for florbetapir in the course of this review. PSUR 14 concluded "Based on the review of new information available in this reporting period and in the context of cumulative knowledge, Lilly concludes that the previously established favourable benefit-risk profile of florbetapir for PET imaging of β-amyloid neuritic plaques in the brains of adult patients with cognitive impairment being evaluated for suspected AD is confirmed. No revisions to the florbetapir reference safety information are warranted at this time".

The tabulated list of adverse reactions in the current approved florbetapir SmPC is as follows, based on the developmental clinical trial safety database at that time of 2105 subjects:

System Organ Class	Common	Uncommon
Nervous system disorders	Headache	Dysgeusia
Vascular disorders		Flushing
Gastrointestinal disorders		Nausea
Skin and subcutaneous tissue disorders		Pruritus Urticaria
General disorders and administration site conditions		Injection site reactiona Infusion site rash

Note: Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000), and not known (cannot be estimated from the available data).

a Injection site reaction includes injection site haemorrhage, injection site irritation, and injection site pain.

Based on the current developmental clinical trial safety database of 5847 subjects, 3 ADR (Headache – 2.1%, Nausea – 0.53%, and Injection site reaction – 0.51%)terms would maintain the same frequency designation and 5 ADR terms (Dysgeusia – 0.02%, Flushing – 0.09%, Pruritus – 0.09%, Urticaria – 0.02%, infusion site rash – 0.02%) would have frequency designations reduced from uncommon to rare.

In taking a more conservative approach to represent the florbetapir safety profile, the marketing authorisation holder has elected not to propose reductions in event frequency categories for SmPC Section 4.8 Undesirable effects.

5.5.2. Discussion on clinical safety

Safety of Amyvid PET in new indication has not been discussed. It is expected that cumulative exposure to radiation will increase through repeated use of Amyvid PET. However, it is assumed that Amyvid will be used for monitoring of treatment effects of amyloid-targeting drugs infrequently (possibly once a year) on the brain amyloid. Further, the SmPC includes warning about the risks of cumulative exposure to radiation and recommends restriction of radiation exposure. Moreover, the medicinal product will be used by the professionals trained adequately, who are aware of radiation-related risks.

Thus, safety risks related to increased radiation exposure are considered generic risks and the warning on cumulative exposure in the SmPC along with the dosimetry information is regarded generally sufficient. A warning regarding increased radiation exposure related to repeated use has been included in the SmPC, which is agreed.

It is not expected that any other safety risks (not radiation-related) may emerge because of repeated use of the product.

Update to section 4.8 of the SmPC:

The Applicant's argumentation explaining the total number of exposed patients and on the frequency of ADRs can be followed. The change is accepted.

Additional expert consultations

Not sought currently.

5.5.3. Conclusions on clinical safety

The change in section 4.8 of the SmPC is endorsed. Safety profile of the product is well-known. No further measures are deemed necessary.

5.5.4. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

6. Risk management plan

The MAH submitted an updated RMP, version 5.1 signed 6 October 2023 (DLP: 06 April 2023) with this application. The main proposed RMP changes were the following:

- conversion of the RMP to align with GVP-Module V Rev. 2 format;
- update of Module SV.1 “Post-authorisation Exposure” to reflect revised labelling to remove the limitation of use regarding monitoring of response to therapy.

Safety Specification

6.1.1. Module SI - Epidemiology of the indications and target population

Module SI has been formatted and completed in accordance with GVP module V rev. 2. The provided information relates to the closest population of the target population of Amyvid, subjects with mild cognitive impairment, and is considered acceptable.

6.1.2. Module SII - Non-clinical Part of the Safety Specification

Module SII has been formatted and completed in accordance with GVP module V rev. 2 and is considered acceptable.

6.1.3. Module SIII - Clinical trial exposure

In Module SIII exposure in clinical trials has been updated in accordance with the revised SmPC submitted in this variation:

A total of 5847 subjects received at least 1 dose of florbetapir. Of these,

- 3778 were considered cognitively impaired subjects (subjects with a clinical diagnosis of AD, MCI, or other dementing disorders);
- 2059 were considered cognitively normal;
- 10 subjects were of unknown cognitive status (Table SIII.5).

There were 811 exposures in subjects of non-Caucasian or unknown ethnic origins. A total of 1074 subjects received at least 2 doses of florbetapir, 246 subjects received at least 3 doses, and 5 subjects received 4 doses.

In 28 pivotal clinical trials of the florbetapir clinical development programme 5847 subjects receiving one or more doses of florbetavir were included in the clinical safety database used for ADR determination, which is acknowledged.

It has been noted that in table S.III.1. “Mean Dose by scan procedure” the number of subjects for “Follow up scan #1” is 1064 instead of 1074, i.e. the number of subjects who received at least two doses of florbetapir. This difference should be corrected or explained in the next RMP update.

Module SIII is considered acceptable.

6.1.4. Module SIV - Populations not studied in clinical trials

The following exclusion criteria in pivotal clinical studies within the development programme are presented in Module SIV:

- clinically significant hepatic impairment;
- clinically significant renal impairment;
- clinically significant cerebrovascular disease;
- neurodegenerative or dementing disease other than AD, including multi-infarct dementia;
- cognitive impairment resulting from other organic causes;
- clinically significant pulmonary, metabolic, endocrine, cardiovascular, infectious or psychiatric disturbances, or history of epilepsy, convulsions, or brain tumour or metastases;
- recent or prior prolonged history of drug or alcohol abuse;
- women of childbearing potential not using adequate contraception;
- history of severe drug allergy or hypersensitivity;
- subjects, who in the last 30 days had received an investigational medicine or participated in a clinical trial, underwent radiation exposure (PET, single-photon emission computed tomography, or computed tomography scans) for experimental purposes within the last year, had received a radiopharmaceutical for imaging or therapy within the 7 days prior to the imaging session, or had a medical condition or history that would confound evaluation of dosimetry;
- taking medications known to cause QT prolongation;
- had a BMI <19 or >32 kg/m^2;
- had ever participated in an experimental study with an amyloid-targeting agent.

A justification to delete “clinically significant hepatic impairment” and “clinically significant cerebrovascular disease” as missing information has been included in line with rev.2 of GVP Module V and can be agreed.

In Table SIV.1. “Ability to Detect Adverse Reactions (Limitation of Trial Programme)” the MAH stated that a total of 1074 subjects received more than one exposure and that no cumulative effects have been identified in this subpopulation. In addition, the MAH explained that TEAES for florbetapir in clinical trials programme compared with subjects with repeated doses are not substantially different and frequency category is the same for each individual AR. However, a slightly higher percentage for some of the TEAEs and ADRs can be seen in patients with repeated doses, e.g. headache (single dose 2.1% vs. repeated dose 4%), dizziness (0.5% vs. 1.1%), nausea (0.5% vs. 0.8%) back pain (0.5% vs. 1.8%) although on a low level.

It is stated in the RMP that repeated florbetapir doses for monitoring response to therapy should be viewed as a series of individual doses spaced at substantial time intervals of several months to several years. Considering florbetapir’s rapid elimination, short half-life and the low effective dose per examination, no cumulative effects having an impact on the benfit-risk balance of the product are to be expected.

Module SIV is considered acceptable.

6.1.5. Module SV - Post-authorisation experience

According to information provided in Module SV, cumulatively, it is estimated that approximately 59.646 patients (49.120 patients in the US, 10.083 patients in the EU, 185 patients in Switzerland,

and 258 patients in the UK [post-exit from the EU]) have been exposed to florbetapir worldwide from 06 April 2012 (the international birth date) through 31 March 2023.

The marketing authorisation holder for Amyvid made the decision to temporarily cease commercial supply of Amyvid for use in routine clinical practice in the EU and Switzerland, as of 29 December 2017. The commercial supply of Amyvid was resumed on 03 November 2020 in Germany, and afterwards temporarily ceased as of 15 March 2021.

Module SV.1 “Post-authorisation Exposure” has been updated to reflect revised labelling to remove the limitation of use regarding monitoring of response to therapy.

Potential for off-label use

In Module SV, section SV.1 “Post-authorisation Exposure” contains the subsection “Post-authorisation off-label use”. Detailed information on study “European Drug Usage Survey for Amyvid” (I6E-MC-AVBF; AVBF) has been removed from this section. In table SV.3 “Estimate risk of MCI progression (non-authorised indication)” is presented as off-label category in the EU. Short information on study AVBF has been included in the Table, which is agreed.

According to the type II variation assessment report on study “European Drug Usage Survey for Amyvid” (AVBF) (EMA Procedure No. EMEA/H/C/002422/II/0029) off-label use was found to be markedly high (63%), primarily for prognostic use and monitoring response to therapy, even after excluding inconsistent responses and using a broader on-label definition.

In the light of these findings, the MAH proposed a change to the SmPC to address further the potential for off-label use of Amyvid. Specifically, it was proposed to increase the prominence of the current “Limitations of Use” statement – including the statement regarding limitations monitoring response to therapy – by repositioning it to the first position in Section 4.4 “Special warnings and precautions for use”, which was supported. Concise information on variation EMEA/H/C/002422/II/0029 is also included in Table SV.3, which is considered adequate.

Module SV is considered acceptable.

6.1.6. Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

It is stated in Module SVI that Florbetapir (18F) has no known pharmacological activity and has very low binding affinity to all central nervous system receptors that have been tested in preclinical screening assays. It is intended to be administered only by appropriately trained medical staff within a hospital environment. The type and amount of radioactivity in the product is also unlikely to have any potential for misuse for illegal purposes. Therefore, it is considered that there is no potential of misuse for illegal purposes.

Based on the substance and mechanism of action, it is agreed that the likelihood for misuse for illegal purposes it is very low. This does not translate to a safety concern that should be addressed in the RMP. Module SVI is considered acceptable.

Module SVI is considered acceptable.

6.1.7. Module SVII - Identified and potential risks

A complete module SVII has been included in the RMP and the following information is presented:

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable, as the initial RMP was written prior to Good Pharmacovigilance Practices Module V revision 2 RMP format.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The MAH stated that this paragraph is not applicable, as this is not the initial RMP.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The MAH stated that this paragraph is not applicable, as this is not the initial RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

The Type II variation assessment report (Committee for Medicinal Products for Human Use and Pharmacovigilance Risk Assessment Committee Rapporteur's preliminary assessment report/Request for Supplementary Information), issued on 06 September 2023 (procedure number: EMEA/H/C/002422/II/0044), has recommended that

- "Hypersensitivity reactions,"
- "Carcinogenicity and hereditary effects,"
- "Safety in patients with hepatic impairment,"
- "Safety in patients with clinically meaningful cerebrovascular diseases"

should not be listed as safety concerns as they are not consistent with GVP Module V, rev.2 criteria. A justification for reclassification has been provided for each concern, which is considered sufficient.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: None

Detailed information is provided for the important potential risks as per GVP Module V Rev. 2:

- Important Potential Risk: PET-imaging interpretation errors

SVII.3.2 Presentation of the Missing Information

The MAH states that there is no missing information for Florbetapir (18F).

The proposed safety concerns are in accordance with criteria provided in GVP Module V Rev. 2.

Module SVII is considered acceptable.

6.1.8. Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	PET-imaging interpretation errors
Missing information	None

"Hypersensitivity reactions" and "Carcinogenicity and hereditary effects" (important potential risks) as well as "Safety in patients with hepatic impairment" and "Safety in patients with clinically meaningful cerebrovascular diseases" (missing information) were deleted from the safety specification, in line with criteria provided in GVP-Module V rev. 2, which is endorsed.

Of note, all of the above safety concerns deleted from the RMP safety specification should be maintained in the safety specification for PSUR purposes. "Cumulative effects after repeated exposure" should be included in the PSUR safety specification as missing information for upcoming PSURs.

Module SVIII is considered acceptable.

Pharmacovigilance plan

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study (Status)	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Not applicable	-	-	-	-
			-	-
Category 2 - Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	-	-	-	-
Category 3 - Required additional pharmacovigilance activities				
Evaluation of Effectiveness of Amyvid Reader Training (I6E-AV-AVBE) *(Ongoing, currently on hold since 2018 due to temporary cessation of commercial supply in the EU)*	Overall objective: • To assess the effectiveness of the reader training programme including different training methods. Primary objectives: • To assess the frequency of reading errors in routine clinical practice	Important potential risk: *PET-imaging interpretation errors*	Protocol endorsed by PRAC, Study is ongoing, currently on hold since 2018 due to temporary cessation of commercial	Interim report submitted 29 Sep 2017. Second interim report submitted: 12 Apr 2018 The study recruitment period will be extended until a total of 30

	after training implementation. • To assess the reader understanding of, and compliance with, the indication with respect to image interpretation after training implementation.		supply in the EU	visual readers are recruited for the "Year 2" group. Quantitative Software Experienced Reader Subgroup (n = 10 readers): When the MAH resumes commercialisation of florbetapir for routine clinical supply in the EU, data collection will commence 6 months after Quant training is initiated in the first EU country. Final report (consisting of Year 1, Year 2, and Quantitative Software Experienced Reader Subgroup) is expected approx. 24 months after initiating quantitative training in the first EU country.

Abbreviations: approx. = approximately; EU=European union; PRAC = Pharmacovigilance Risk Assessment Committee.

Generally, the MAH has discussed how the safety concerns from Module SVIII will be addressed within the pharmacovigilance plan.

The study "Evaluation of Effectiveness of Amyvid Reader Training" (I6E-AV-AVBE) is in the correct category (3). This study is on hold since 2018 due to temporary cessation of commercial supply in the EU.

According to the evaluation of the second interim report after Year 2 (Year 1 and Year 2 assessment) submitted on 12 April 2018, reader's understanding of and compliance with the indication was overall high. Regarding Amyvid image interpretation the performance of readers in the clinical setting is comparable to the results of the clinical trials. However, results in the subcategory "impression" was comparatively low and decreased from Year 1 to Year 2. Furthermore, almost one third of readers had a FPR over 20% when interpreting scan images. The number of recruited physicians in the online training cohort was too small for statistical comparison with the in-person cohort.

A final conclusion on the suitability of the Amyvid reader training to ensure that accuracy in routine clinical practice is in line with the expected accuracy from the clinical trials as well as a conclusion on the comparability of in-person and online training will depend on the final results including at least 16 additional readers for the Year 2 group, for a total of 30 visual readers, and data of readers experienced in using quantitation software which has been demonstrated to augment the existing visual read and has the potential to improve reader accuracy.

It was further concluded, that when the MAH resumes commercialisation of florbetapir for routine clinical supply in the EU, data collection for study I6E-AV-AVBE will commence six months after quantitative training is initiated in the first EU country. Reader enrolment and data collection will continue until 10 readers are enrolled, approximately 15 months after the start of data collection. Data analysis and final report are anticipated to require three months from completion of data collection. The results from the final analysis comprising Year 1, Year 2 (including at least 16 additional readers) and the results of a subgroup of readers trained and experienced in using quantitation software should be submitted as part of a final report on study results as a follow-up to the respective MEA 24 months after initiating quantitative training in the first EU country. In the group of readers experienced in quantitative reading, 10 readers will be recruited.

Final study results are considered to be useful to evaluate the effectiveness of the Amyvid reader training. The MAH is reminded that recruitment should not be ceased once the additional 16 physicians participate in the study as 25 readers in each country for each year of assessment were originally intended as per protocol. Moreover, recruitment should ensure that a higher number of readers trained online is included to balance both groups, in-person and online trained participants.

According to the MAH the Evaluation of Effectiveness of Amyvid Reader Training Study (AVBE) is currently on hold since 2018 due to temporary cessation of commercial supply in the EU. The MAH should consider the impact of the extension of indication for the monitoring of response to amyloid-targeting therapy and the removal of the monitoring response to therapy limitation from Section 4.4 of the SmPC on study AVBE. The study protocol shoud be amended accordingly before study re-initiation.

Part III is considered acceptable.

Overall conclusions on the PhV Plan

There are still outstanding issues regarding the RMP, but a preliminary view is that:

The study in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

The MAH should consider the impact of the extension of indication for the monitoring of response to amyloid-targeting therapy and the removal of the monitoring response to therapy limitation from Section 4.4 of the SmPC on study AVBE. The study protocol should be amended accordingly before study re-initiation.

Risk minimisation measures

V.1. Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
PET imaging interpretation errors	Routine risk communication: SmPC Sections 4.2 and 4.4 Section 4.2 emphasises that interpretations of amyloid PET images should only be performed by appropriately trained readers. Section 4.4 details potential limitations when interpretating amyloid PET images. Other routine risk minimisation measures beyond the product information: Legal status: Restricted medical prescription.

Abbreviations: PET = positron emission tomography; SmPC = summary of product characteristics.

Additional risk minimisation measures

A physician reader training was considered needed for the safe and effective use of the product as an additional risk minimisation measure during granting of the marketing authorisation regarding the important potential risk “PET imaging interpretation errors” and is presented in the RMP as follows:

Additional risk minimisation measure: Physician/Reader Training Programme

Objective: Physicians reading the scans must be trained in interpreting the images from PET scans of florbetapir (18F) to avoid incorrect interpretation of images, which may lead to subsequent inappropriate patient management. The aim is to minimise the occurrence of false positive and false negative interpretations.

The training program includes:

information on amyloid pathology in Alzheimer's disease

review of the PET reading criteria

florbetapir PET demonstration cases with correct PET scan interpretation by an experienced reader, and

florbetapir PET scans for practice interpretation and self-assessment.

Risk addressed:

PET imaging interpretation errors.

Rationale for the additional risk minimisation activity:

Training to optimise interpretation of PET scan.

Target audience and planned distribution path:

The intended audience for the reader training programme is physicians trained in nuclear medicine or physicians trained in radiology with additional training or commensurate experience in nuclear medicine.

Delivery of the training programme to interpreting physicians will be achieved by Lilly-sponsored electronic (online) training sessions and national and regional medical education symposia (in-person).

Plans to evaluate the effectiveness of the interventions and criteria for success:

EU Study AVBE, Evaluation of Effectiveness of Amyvid Reader Training, will determine the frequency of errors in the effectiveness study and will be deemed successful if consistent with that observed in clinical trials. Study AVBE is currently on hold since 2018 due to temporary cessation of commercial supply in the EU.

Removal of additional risk minimisation materials:

Not applicable.

V.3 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
PET imaging interpretation errors	SmPC Sections 4.2 and 4.4 Section 4.2 emphasises that interpretations of amyloid PET images should only be performed by appropriately trained readers. Section 4.4 details potential limitations when interpretating amyloid PET images Additional risk minimisation measures: Training to optimise interpretation of PET scan.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional Pharmacovigilance Activities: Evaluation of effectiveness of Amyvid reader training.

The extension of indication for the monitoring of response to amyloid-targeting therapy and the removal of the monitoring response to therapy limitation from Section 4.4 of the SmPC has an impact on the eduational material since „information on (…) the approved indication according to the SmPC“ is a key element of the educational material. Therefore, the educational material should be amended accordingly.

Part V is considered acceptable.

Overall conclusions on risk minimisation measures

There are still outstanding issues regarding the RMP but a preliminary view is that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The extension of indication for the monitoring of response to amyloid-targeting therapy and the removal of the monitoring response to therapy limitation from Section 4.4 of the SmPC has an impact on the educational material since „information on (…) the approved indication according to the SmPC“ is a key element of the educational material. Therefore, the educational material should be amended accordingly.

Elements for a public summary of the RMP

The elements for a public summary of the RMP require do not require revision.

Part VI is considered acceptable.

Annexes

The annexes have been updated appropriately and are considered acceptable.

Overall conclusion on the RMP

The RMP, version 5.1 signed 6 October 2023 (DLP: 06 April 2023) is considered approvable.

The difference in the number of subjects in table S.III.1. “Mean Dose by scan procedure” - “Follow up scan #1”, 1064, and the number of subjects who received at least two doses of florbetapir, 1074, should be corrected or explained in the next RMP update.

The MAH should consider the impact of the extension of indication for the monitoring of response to amyloid-targeting therapy and the removal of the monitoring response to therapy limitation from Section 4.4 of the SmPC on study AVBE. The study protocol shoud be amended accordingly before study re-initiation.

The extension of indication for the monitoring of response to amyloid-targeting therapy and the removal of the monitoring response to therapy limitation from Section 4.4 of the SmPC has an impact on the educational material since „information on (…) the approved indication according to the SmPC“ is a key element of the educational material. Therefore, the educational material should be amended accordingly.

“Hypersensitivity reactions” and “Carcinogenicity and hereditary effects” (important potential risks) as well as “Safety in patients with hepatic impairment” and “Safety in patients with clinically meaningful cerebrovascular diseases” (missing information) should be maintained in the safety specification for PSUR purposes. “Cumulative effects after repeated exposure” should be included in the PSUR safety specification as missing information for upcoming PSURs.

7. Changes to the Product Information

As a result of this variation, section(s) 4.1, 4.4 and 4.8 of the SmPC are being updated to reflect the new indication claimed. The Package Leaflet (PL) is updated accordingly. Further minor adaptations were made to section 1.

The Product Information will require adaptation after the requested data are provided (see the MO from the second RSI).

7.1.1. User consultation

Full user testing was done and accepted for initial MAA. Currently included adaptations in the PL are minor. Overall, the structure and design of the revised Amyvid Package Leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability. Therefore, Lilly did not consider it necessary to conduct further consultation with target patient groups further to that performed for the initial MAA. This is agreed.

8. Benefit-Risk Balance

8.1. Therapeutic Context

AD remains broadly spread disease without approved effective treatment in the EU. Currently, large number of new active substances are being in development for treatment of AD. MAA has been submitted to the EMA for two of these, including a product by the Applicant (donanemab – Kisunla by Eli Lilly Nederland B.V.; Procedure number EMEA/H/C/006064), and review is ongoing. If approved, one of the possibilities to monitor treatment effects in the patients on amyloid-targeting therapies would be amyloid PET, e.g., Amyvid PET.

None of the three EU-approved Aβ amyloid PET tracers Amyvid (the product under evaluation), Vizamyl MA (Flutemetamol 18F; EMEA/H/C/002557; approved in 2014) and Neuraceq (Florbetaben (18F) by Life Molecular Imaging GmbH; EMEA/H/C/002553; approved in 2014) have been approved for monitoring of treatment effects on the brain amyloid. If this variation is approved, Amyvid PET would be the first to offer the option of treatment monitoring.

The new indication applied for is

Imaging of β-amyloid neuritic plaque density in the brains of adult patients receiving amyloid-targeting therapy

8.2. Favourable effects

Florbetapir PET can be able to detect changes in the amyloid burden in patients treated with amyloid-targeting treatment.

8.3. Uncertainties and limitations about favourable effects

The evidence is burdened by a number of limitations and uncertainties:

- lack of a well-designed and adequately controlled studies to support the indication and difficulty to extrapolate diagnostic efficacy from the approve indication to the new one. A reader study is requested. (MO)
- generalisability of the effects across amyloid-targeting treatments unclear. Therefore, addition of the information that data are mainly limited to donanemab is proposed. (OC)
- methodologies to monitor treatment effects is not acceptable as it does not reflect state of the art. Development of the dedicated methodology is requested.
- the Applicant has not provided concrete data on the impact on patient management or diagnostic confidence for Florbetapir. However, it is acknowledged that in the absence of approved amyloid targeted treatment, collection of such data may be challenging. Moreover, it is apparent that amyloid PET is being actively used in monitoring of AAT effects as a PD parameter. If approved, Florbetapir PET may be utilised for decision-making on treatment discontinuation.
- reliability of the test in the new targeted clinical setting is unclear (test/re-test, inter and intra-reader variability). A reader study is requested. (MO)
- potential confounders which could impact accurate reading of Amyvid images have not been discussed. A reader study is requested. (MO)

8.4. Unfavourable effects

Increased exposure through repeated use is expected.

8.5. Uncertainties and limitations about unfavourable effects

None.

8.6. Effects Table

Not applicable.

8.7. Benefit-risk assessment and discussion

8.7.1. Importance of favourable and unfavourable effects

If proven accurate, use of Amyvid PET in monitoring the effects of amyloid-targeting treatments on β amyloid burden would contribute to patient care considerably, provided that such treatments are approved.

Although, increased radiation exposure is expected, repeated scans will likely be conducted infrequently. Cumulative radiation exposure has been addressed in the SmPC as topic for consideration. Additional warning has been included.

8.7.2. Balance of benefits and risks

Currently, proof of efficacy is missing and needs to be provided. Thus, benefits have not been established yet. There are no relevant risks related to the repeated use of the product, provided that the product is used following the rules relevant for radiation protection.

8.7.3. Additional considerations on the benefit-risk balance

N/A

8.8. Conclusions

The overall B/R of Amyvid is negative.