24 July 2025
EMADOC-1700519818-2276977
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Neuraceq

International non-proprietary name: Florbetaben (18F)

Procedure No. EMA/VR/0000227744

Marketing Authorisation Holder (MAH): Life Molecular Imaging GmbH

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List of abbreviations

AD	Alzheimer's Disease
AMYPAD	Amyloid Imaging to Prevent Alzheimer's Disease
ARIA	Amyloid-related imaging abnormalities
ATT	Amyloid-targeting therapy
CE	Conformité Européenne
CL	Centiloid
CHMP	Committee for Medicinal Products for Human Use
CSF	Cerebrospinal fluid
DMD	Disease Modifying Drug
DPMS	Diagnostic and Patient Management Study
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDG	Fludeoxyglucose (18F)
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GAAIN	Global Alzheimer's Association Interactive Network
mCRPC	Metastatic castration-resistant prostate cancer
MAPT	Multidomain Alzheimer Preventive Trial
PET	Positron Emission Tomography
PSMA	Prostate-specific membrane antigen
SUVR	Standardized Uptake Value Ratio
SmPC	Summary of Product Characteristics
USPI	US Package Insert
QIBA	Quantitative Imaging Biomarkers Alliance
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Life Molecular Imaging GmbH submitted to the European Medicines Agency on 27 August 2024 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include monitoring of the biological treatment response to pharmacological and non-pharmacological interventions for Neuraceq, based on supporting literature. As a consequence, sections 4.1, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.91 of the RMP has also been submitted. In addition, the MAH took the opportunity to include the proposal to discontinue the inclusion of a paper copy of the SmPC with the product package.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/193/2011 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Antonio Gomez-Outes Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 August 2024
Start of procedure	14 September 2024
CHMP Rapporteur assessment report	8 November 2024
PRAC Rapporteur assessment report	15 November 2024

Timetable	Actual dates
PRAC comments	20 November 2024
PRAC outcome	28 November 2024
CHMP comments	2 December 2024
Updated Joint Rapporteur's assessment report	5 December 2024
1st Request for supplementary information and extension of timetable adopted by the CHMP on	12 Decembre 2024
MAH's responses submitted on	24 February 2025
Re-start date	25 February 2025
CHMP Rapporteur assessment report	31 March 2025
PRAC Rapporteur assessment report	27 March 20225
PRAC comments	28 March 2025
PRAC outcome	10 April 2025
CHMP comments	14 April 2025
Updated Joint Rapporteur's assessment report	16 April 2025
2nd request for supplementary information and extension of timetable adopted by the CHMP on	25 April 2025
MAH's responses submitted on	20 June 2025
Re-start date	25 June 2025
CHMP Rapporteur assessment report	08 July 2025
PRAC Rapporteur assessment report	26 June 2025
PRAC comments	02 July 2025
CHMP comments	14 July 2025
Updated Joint Rapporteur's assessment report	18 July 2025
CHMP opinion	24 July 2025

2. Scientific discussion

2.1. Introduction

Neuraceq, florbetaben (18F), 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. Neuraceq should be used in conjunction with a clinical evaluation.

With this variation, based on published literature, the MAH is seeking approval for an extension of indication for Neuraceq to include monitoring of the biological treatment response to pharmacological and non-pharmacological interventions based on supporting literature.

2.2. Non-clinical aspects

A non-clinical *in-vitro* study consisting of three complementary methods (immunohistochemistry, autoradiography and ligand-binding assays) to investigate potential interactions between florbetaben (18F) and lecanemab has been submitted.

2.3. Clinical aspects

2.4. Clinical efficacy

The most relevant publications provided to support this variation are:

- Therapy monitoring of amyloid beta-directed antibodies

1. Gantenerumab: GRADUATE I and II studies (Bateman et al., 2023).

2. Aducanumab: EMERGE and ENGAGE studies (Budd Haeberlein et al. 2022).

3. Lecanemab: two studies, CLARITY AD study (van Dyck et al., 2022) and Lecanemab study 201 core and OLE (McDade et al., 2022).

4. Donanemab: TRAILBLAZER-ALZ 2 study (Sims et al., 2023).

- Amyloid-PET in non-pharmacological interventions

1. FINGER study in at-risk elderly people (Ngandu T. et al., 2015).

2. MAPT study in elderly adults with memory complaints (Andrieu S. et al., 2017).

THERAPY MONITORING OF AMYLOID BETA-DIRECTED ANTIBODIES.

1. Gantenerumab: GRADUATE I and II studies (Bateman et al., 2023).

GRADUATE I and II were two phase 3 multicenter, randomized, double-blind, placebo controlled, parallel-group trials involving participants 50 to 90 years of age with mild cognitive impairment or mild dementia due to Alzheimer's disease and evidence of amyloid plaques on positron-emission tomography (PET) or cerebrospinal fluid (CSF) testing.

Participants were randomly assigned to receive gantenerumab or placebo every 2 weeks. The primary outcome was the change from baseline in the score on the Clinical Dementia Rating scale–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater cognitive impairment) at week 116.

Some participants were enrolled in substudies that involved longitudinal cerebrospinal fluid (CSF) evaluation for amyloid, PET evaluation for amyloid, or PET evaluation for tau; these substudies were conducted to evaluate the effect of gantenerumab on brain amyloid and tau levels. CSF evaluation was conducted only at sites where lumbar puncture could be performed.

In the amyloid PET substudy, the main outcome was the change from baseline to week 116 in the amyloid level. The amyloid level was assessed on florbetaben (18F) or flutemetamol (18F) PET and

was measured as a standardized uptake value ratio (SUVR), which is the ratio of the standardized uptake value in the composite region of interest to the value in the inferior cerebellar cortex; the SUVR results were converted to centiloids.

RESULTS: A total of 985 and 980 participants were enrolled in the GRADUATE I and II trials, respectively. The baseline CDR-SB score was 3.7 in the GRADUATE I trial and 3.6 in the GRADUATE II trial. The change from baseline in the CDR-SB score at week 116 was 3.35 with gantenerumab and 3.65 with placebo in the GRADUATE I trial (difference, −0.31; 95% confidence interval [CI], −0.66 to 0.05; P = 0.10) and was 2.82 with gantenerumab and 3.01 with placebo in the GRADUATE II trial (difference, −0.19; 95% CI, −0.55 to 0.17; P = 0.30).

The amyloid level on PET at week 116 among participants receiving gantenerumab was lower than the level among those receiving placebo (Figure 1). The difference in the adjusted mean (±SE) amyloid level between the gantenerumab group and the placebo group was −66.44±4.17 centiloids (95% CI, −74.71 to −58.16) in the GRADUATE I trial and −56.46±3.98 centiloids (95% CI, −64.36 to −48.56) in the GRADUATE II trial. The mean (±SD) amyloid level at week 116 was 40.68±27.39 and 104.44±33.15 centiloids in the gantenerumab and placebo groups, respectively, in the GRADUATE I trial and 44.85±26.67 and 99.52±27.72 centiloids in the gantenerumab and placebo groups, respectively, in the GRADUATE II trial.

At week 116, amyloid-negative status (amyloid level, ≤24 centiloids) was attained in 28.0% and 2.4% of the participants receiving gantenerumab and placebo, respectively, in the GRADUATE I trial and in 26.8% and none of the participants receiving gantenerumab and placebo, respectively, in the GRADUATE II trial. A post hoc exploratory analysis of clinical response in participants who had attained amyloid-negative status was performed. No definitive conclusions can be drawn from the findings.

There was no appreciable difference between the gantenerumab group and the placebo group in the tau level assessed in any of the four composite regions on PET at week 116. For example, the between-group difference in the median SUVR assessed in the medial temporal composite region, which did not include the hippocampus, was −0.02 (95% CI, −0.06 to 0.03) in the GRADUATE I trial and 0.04 (95% CI, −0.03 to 0.09) in the GRADUATE II trial.

Figure 1 : Biomarker outcomes

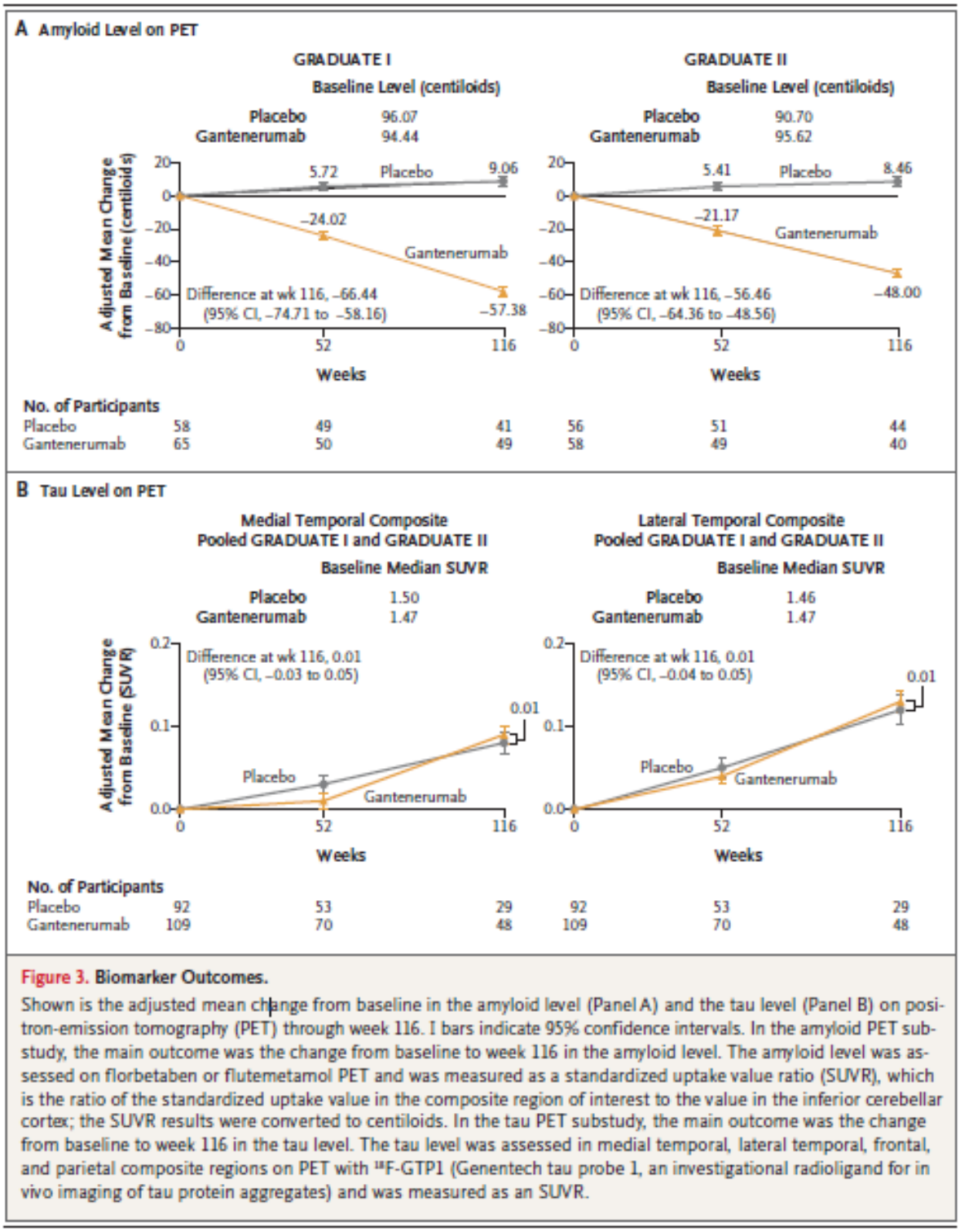


Figure 3. Biomarker Outcomes.

Shown is the adjusted mean change from baseline in the amyloid level (Panel A) and the tau level (Panel B) on positron-emission tomography (PET) through week 116. I bars indicate 95% confidence intervals. In the amyloid PET substudy, the main outcome was the change from baseline to week 116 in the amyloid level. The amyloid level was assessed on florbetaben or flutemetamol PET and was measured as a standardized uptake value ratio (SUVR), which is the ratio of the standardized uptake value in the composite region of interest to the value in the inferior cerebellar cortex; the SUVR results were converted to centiloids. In the tau PET substudy, the main outcome was the change from baseline to week 116 in the tau level. The tau level was assessed in medial temporal, lateral temporal, frontal, and parietal composite regions on PET with ^{18}F-GTP1 (Genentech tau probe 1, an investigational radioligand for in vivo imaging of tau protein aggregates) and was measured as an SUVR.

Author´s conclusion: Among persons with early Alzheimer's disease, the use of gantenerumab led to a lower amyloid plaque burden than placebo at 116 weeks but was not associated with slower clinical decline.

2. Aducanumab EMERGE and ENGAGE studies (Budd Haeberlein et al. 2022).

EMERGE (NCT02484547) and ENGAGE (NCT02477800) were two randomized, double-blind, placebo-controlled, global, phase 3 studies of aducanumab in patients with early Alzheimer's disease to evaluate the efficacy and safety of aducanumab in early Alzheimer's disease.

Participants included 1638 (EMERGE) and 1647 (ENGAGE) patients aged 50 to 85 years who met clinical criteria for MCI due to AD (Albert MS et al., 2011) or mild AD dementia (McKhann et al., 2011), with amyloid pathology confirmed by visual assessment of amyloid positron emission tomography (PET; 18F-florbetapir, 18F-flutemetamol, or 18F-florbetaben).

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.

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]). Results of biomarker substudies confirmed target engagement and dose-dependent reduction in markers of Alzheimer's disease pathophysiology. The most common adverse event was amyloid-related imaging abnormalities-edema.

Author's 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.

3. Lecanemab: two studies, CLARITY AD study (van Dyck et al., 2022) and McDade et al., 2022)

- **CLARITY AD study (van Dyck et al., 2022)**

Clarity AD was an 18-month, multicenter, double-blind, placebo-controlled, parallel-group phase 3 trial involving persons 50 to 90 years 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.

Eligible participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram every 2 weeks) or placebo. The randomization was stratified according to clinical subgroup (mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease–related dementia on the basis of the criteria noted below), the presence or absence of concomitant approved medication for symptoms of Alzheimer's disease at baseline (e.g., acetylcholinesterase inhibitors, memantine, or both), apolipoprotein E (ApoE) ε4 carriers or noncarriers, and geographic region. 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 cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease.

The primary efficacy endpoint (**Figure 2**) was the change in the score on the Clinical Dementia Rating (CDR)–Sum of Boxes (CDR-SB) from baseline at 18 months. The CDR-SB score is a validated outcome measure used in clinical trials of Alzheimer's disease that is obtained by interviewing patients and their care partners and captures cognition and function. It assesses six domains that patients and caregivers identify as important (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care). Scores for each domain range from 0 to 3, with higher scores indicating greater impairment. Total scores range from 0 to 18, with a score of 0.5 to 6 indicating early Alzheimer's disease.

Key secondary end points (Figure 2) 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 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 neurofilament 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 have not been fully analyzed.

A prespecified exploratory and multiplicity unadjusted analysis examined the time to worsening of the global CDR score (range, 0 to 3, with higher scores indicating greater impairment). This end point was defined as the time to the first increase of at least 0.5 points in the global CDR score on two consecutive visits.

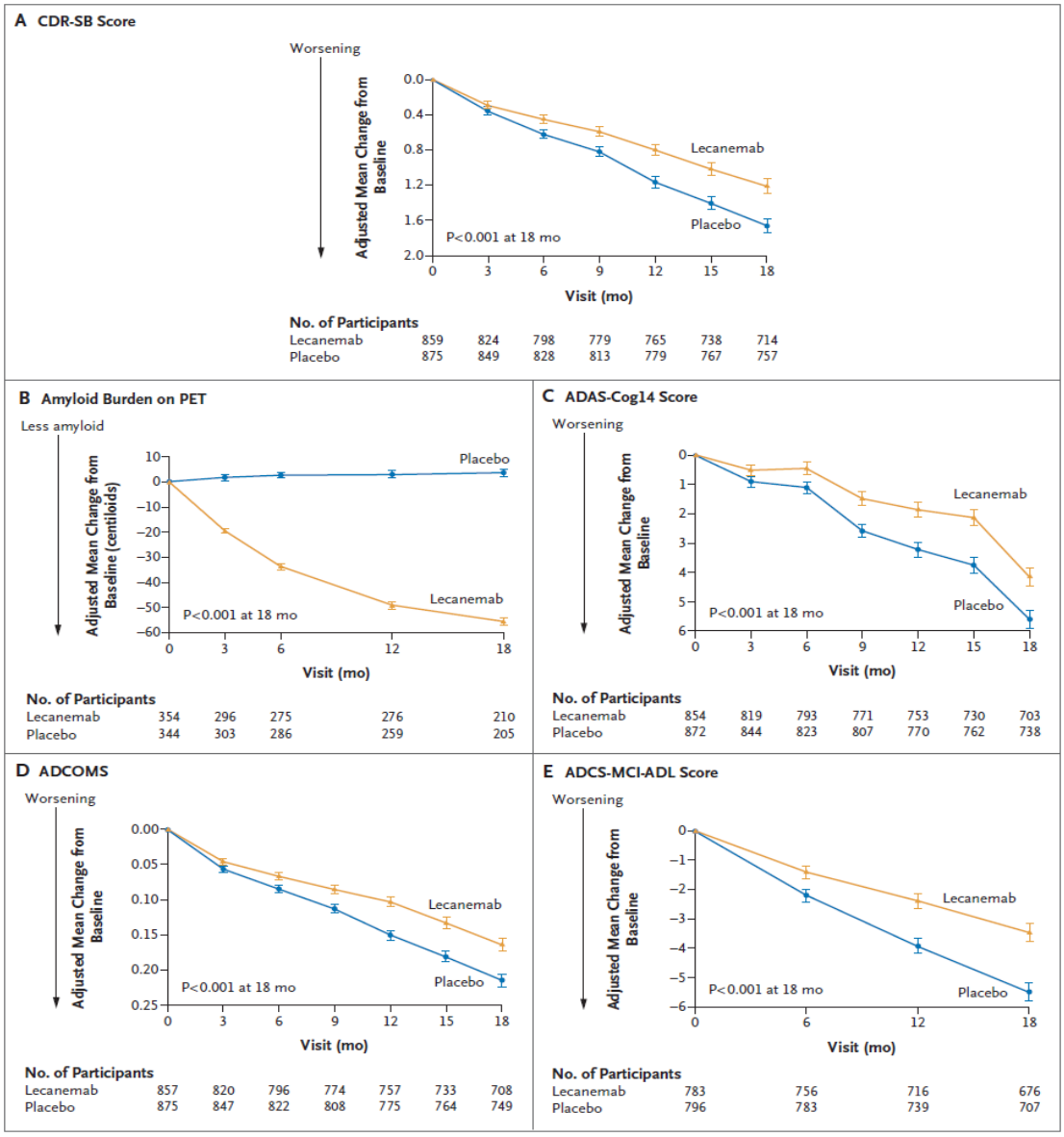
RESULTS: A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001).

In the substudy of amyloid burden on PET (a key secondary end point) involving 698 participants, the mean amyloid level at baseline was 77.92 centiloids in the lecanemab group and 75.03 centiloids in the placebo group. In this substudy there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, −59.1 centiloids; 95% CI, −62.6 to −55.6). Other mean differences between the two groups in the change from baseline favoring 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-MCIADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001).

After 18 months of treatment in the amyloid substudy, the mean amyloid level of 22.99 centiloids in the lecanemab group was below the threshold for amyloid positivity of approximately 30 centiloids, above which participants are considered to have elevated brain amyloid levels.

Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.

Figure 2. Primary and key secondary endpoints



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.

-**Lecanemab study 201 core and OLE (McDade et al., 2022)**

The lecanemab study 201 core was a double-blind, randomized, placebo-controlled study of 856 patients randomized to one of five dose regimens or placebo. An open-label extension (OLE) of study 201 was initiated to allow patients to receive open-label lecanemab 10mg/kg biweekly for up to 24 months, with an intervening off-treatment period (gap period) ranging from 9 to 59 months (mean 24 months).

At entry into the core study, subjects were required to have early AD (amyloid positive) with global Clinical Dementia Rating (CDR) global score of 0.5 or 1. Subjects were randomized to either

placebo or one of 5 active arms of lecanemab (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, 10 mg/kg biweekly) without titration. Treatment duration of the study was 18 months with a 3-month follow-up and a target enrollment of approximately 800 subjects.

The primary outcome was based on a Bayesian analysis at 12 months; the study continued per protocol with no unblinding to month 18. To maintain the blind during the double-blind portion of the trial, all subjects received biweekly infusions of either placebo or lecanemab.

Study assessments for the study 201 core and OLE included the Alzheimer's Disease Composite Score (ADCOMS); Clinical Dementia Rating Sum-of-Boxes (CDR-SB); Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14); changes in plasma biomarkers; and brain amyloid by PET Standardized Uptake Value ratio (SUVr) (in an optional substudy of consenting participants). The core amyloid PET substudy assessed baseline, 12-month, and 18-month SUVr with florbetapir; the OLE amyloid PET substudy assessments were at baseline, 3 or 6 months, 12 and 24 months. Plasma samples were collected at the same timepoints as the PET studies. Imaging (PET with 18F-florbetapir tracer) and plasma (amyloid-β (Aβ)42/40 ratio, phospho-tau (p-tau)181) biomarkers were evaluated. The amyloid PET SUVr normalized to whole cerebellum mask, measured using [18]F florbetapir as a PET ligand, was used to determine brain amyloid levels.

RESULTS: The PET substudy included 315 subjects in core and 91 in OLE (22, 21, and 48 having received placebo, lecanemab 10 mg/kg biweekly, or a different lecanemab dose in the core, respectively).

The results from the primary analysis of the study 201 core phase, including clinical efficacy and biomarkers, have previously been published. Briefly, lecanemab treatment resulted in reduction in brain amyloid accompanied by a consistent reduction of clinical decline across several clinical and biomarker endpoints. The least squares (LS) mean change from baseline in brain amyloid levels as measured by amyloid PET SUVr and in Centiloid scales are shown in the following Figure 3.

Figure 3. Results for a amyloid PET SUVr and B centiloid scale assessments from study 201 core

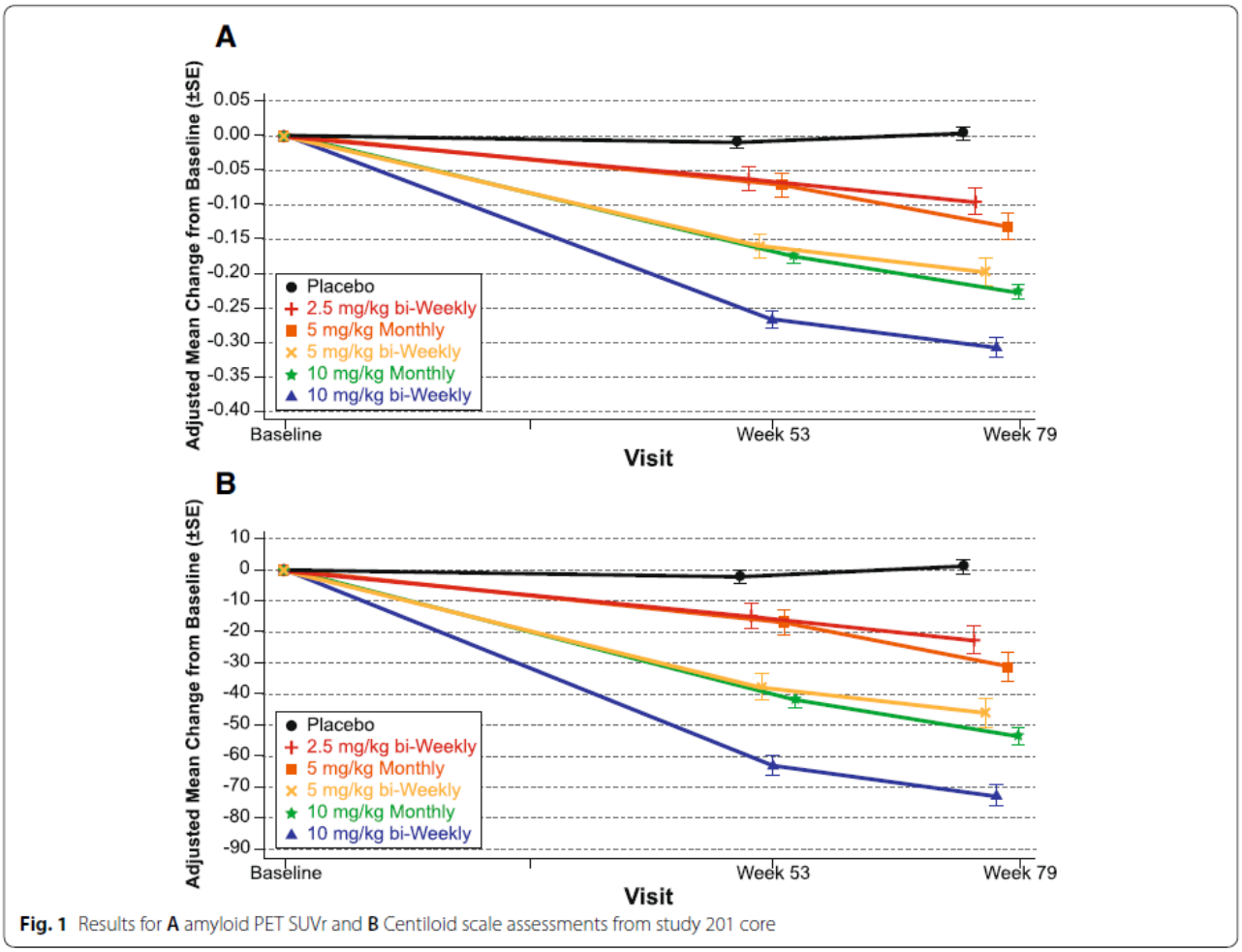


Fig. 1 Results for **A** amyloid PET SUVr and **B** Centiloid scale assessments from study 201 core

Lecanemab demonstrated a dose-dependent and time-dependent brain amyloid reduction across all doses versus placebo. Overall, 65% of subjects at 12 months and 81% of subjects at 18 months converted from amyloid positive to amyloid negative by visual read.

The reduction in brain amyloid with lecanemab treatment as measured by amyloid PET Centiloids was associated with a slowing in clinical decline measured on the CDR-SB at the population level (Pearson correlation coefficient=0.802, P=0.103; and subject level (Pearson correlation coefficient=0.119, P=0.059). Similar PET SUVr relationships were seen for ADCOMS at the population level (Pearson correlation coefficient=0.835, P=0.079; and subject level (Pearson correlation coefficient=0.128, Pearson correlation coefficient=0.695, P=0.192) and subject level (Pearson correlation coefficient= 0.057, P=0.373).

The relationship between change of amyloid PET SUVr and clinical efficacy endpoints was explored with model-predicted CFB of PET SUVr evaluated as a predictor of the efficacy endpoints. Disease progression rates for CdR-SB, ADCOMS, and ADAS-Cog14 were reduced by 11.6, 10.1, and 10.3% for every 20 centiloids reduction from baseline PET. Model predicted reduction from baseline PET over 18 months of lecanemab 10 mg/kg biweekly was 60.1 CL; the corresponding model predicted reductions of disease progression rates in CDR-SB, ADCOMS, and ADAS-Cog14 were 34.8, 30.2, and 31.0%, respectively.

In the OLE, brain amyloid is statistically significantly reduced relative to OLE phase baseline after as little as 3 months of treatment as measured by amyloid PET SUVr and Centiloid scales, with continued brain amyloid reduction through 24 months of treatment, in subjects who received prior placebo and those who were treated with lecanemab 10 mg/kg biweekly in study 201 core In subjects on placebo in the core study who began lecanemab therapy at the start of the OLE, amyloid status by visual read converted from positive to negative in 43% (3/7) by 3 months (week 13), 75% (6/8) by the 6-month visit (week 27), 83% (10/12) by the 12-month visit (week 53) and 80% (4/5) by the 24-month visit (week 105). The findings for conversion to amyloid negative were similar when assessed by amyloid PET SUVr and Centiloid scales.

In the OLE, ADCOMS, CDR-SB, and ADAS-Cog14 scores continued to increase in both newly treated core placebo subjects and in those retreated with lecanemab. Greater reduction in brain amyloid as measured by amyloid PET SUVr was associated with greater slowing of clinical decline across clinical efficacy scores.

Among the subjects that participated in both study 201 core and the OLE phase, change from core baseline in brain amyloid levels as measured by amyloid PET SUVr increased slightly in the placebo group during study 201 core and was markedly decreased with lecanemab 10 mg/kg biweekly, consistent with the overall core study results. Amyloid PET SUVr data indicate that amyloid levels reaccumulated slightly in all subjects while off treatment over the gap period, consistent with expected natural history of amyloid accumulation rates in AD. Thus, treatment discontinuation resulted in return towards pre-treatment in plasma Aβ42/40 ratio, p-tau181, and amyloid PET SUVr, recapitulating the progression of the amyloid cascade.

Author's conclusions: In summary, an increase in exposure to lecanemab resulted in significant and clinically relevant reductions in PET SUVr and slowing of clinical decline. Lecanemab treatment resulted in significant reduction in amyloid plaques and a slowing of clinical decline. Data indicate that rapid and pronounced amyloid reduction correlates with clinical benefit and potential disease-modifying effects, as well as the potential to use plasma biomarkers to monitor for lecanemab treatment effects.

4. Donanemab: TRAILBLAZER-ALZ 2 study (Sims et al., 2023).

TRAILBLAZER-ALZ 2 study was a multicenter (277 medical research centers/hospitals in 8 countries), randomized, double-blind, placebo-controlled, 18-month phase 3 trial to assess efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque.

The study enrolled 1736 participants aged 60 to 85 years with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on positron emission tomography imaging from June 2020 to November 2021. Eligible participants had screening Mini-Mental State Examination (MMSE) scores of 20 to 28, amyloid pathology (≥37 Centiloids) assessed with 18F-florbetapir or 18F-florbetaben positron emission tomography (PET), and presence of tau pathology assessed by 18F-flortaucipir PET imaging with central image evaluation.

Screening procedures also included magnetic resonance imaging (MRI), and key exclusion criteria included presence of amyloid-related imaging abnormalities (ARIA) of edema/effusion, more than 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, and any intracerebral hemorrhage greater than 1 cm or severe white matter disease on MRI.

Eligible participants were randomly assigned in a 1:1 ratio either to receive 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 (TRAILBLAZER-ALZ cutoffs), donanemab was switched to placebo in a blinded procedure. Final adverse events and efficacy assessments were performed at 76 weeks. Amyloid-related imaging abnormality monitoring occurred with scheduled MRIs at 4, 12, 24, 52, and 76 weeks and unscheduled MRIs at investigator discretion. Any participant with detected amyloid-related imaging abnormalities had imaging every 4 to 6 weeks until resolution or stabilization. Amyloid-related imaging abnormality management and treatment interruption guidelines depended on severity and symptoms.

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. The iADRS is an integrated assessment of cognition and daily function from the 13-item cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog13) and Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living (ADCS-iADL), measuring global disease severity across the Alzheimer disease continuum as a single summary score. The iADRS is validated and captures clinical progression from MCI due to Alzheimer disease through moderate dementia due to Alzheimer disease, and treatment effects have been demonstrated across MCI and Alzheimer disease with mild dementia. The possible scores on the iADRS range from 0 to 144 (lower scores indicate greater impairment), and the meaningful within patient change (MWPC) is a change of 5 points for those with Alzheimer disease with MCI and 9 points for those with Alzheimer disease with mild dementia.

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, 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 (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.

The least-squares mean (LSM) change in 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) in the low/medium tau population and −10.2 (95%CI, −11.22 to −9.16) with donanemab and −13.1 (95%CI, −14.10 to −12.13) with placebo (difference, 2.92 [95%CI, 1.51-4.33]; P < .001) in the combined population.

LSM change in CDR-SB score at 76 weeks was 1.20 (95%CI, 1.00-1.41) with donanemab and 1.88 (95%CI, 1.68-2.08) with placebo (difference, −0.67 [95%CI, −0.95 to −0.40]; P < .001) in the low/medium tau population and 1.72 (95%CI, 1.53-1.91) with donanemab and 2.42 (95%CI, 2.24-2.60) with placebo (difference, −0.7 [95%CI, −0.95 to −0.45]; P < .001) in the combined population.

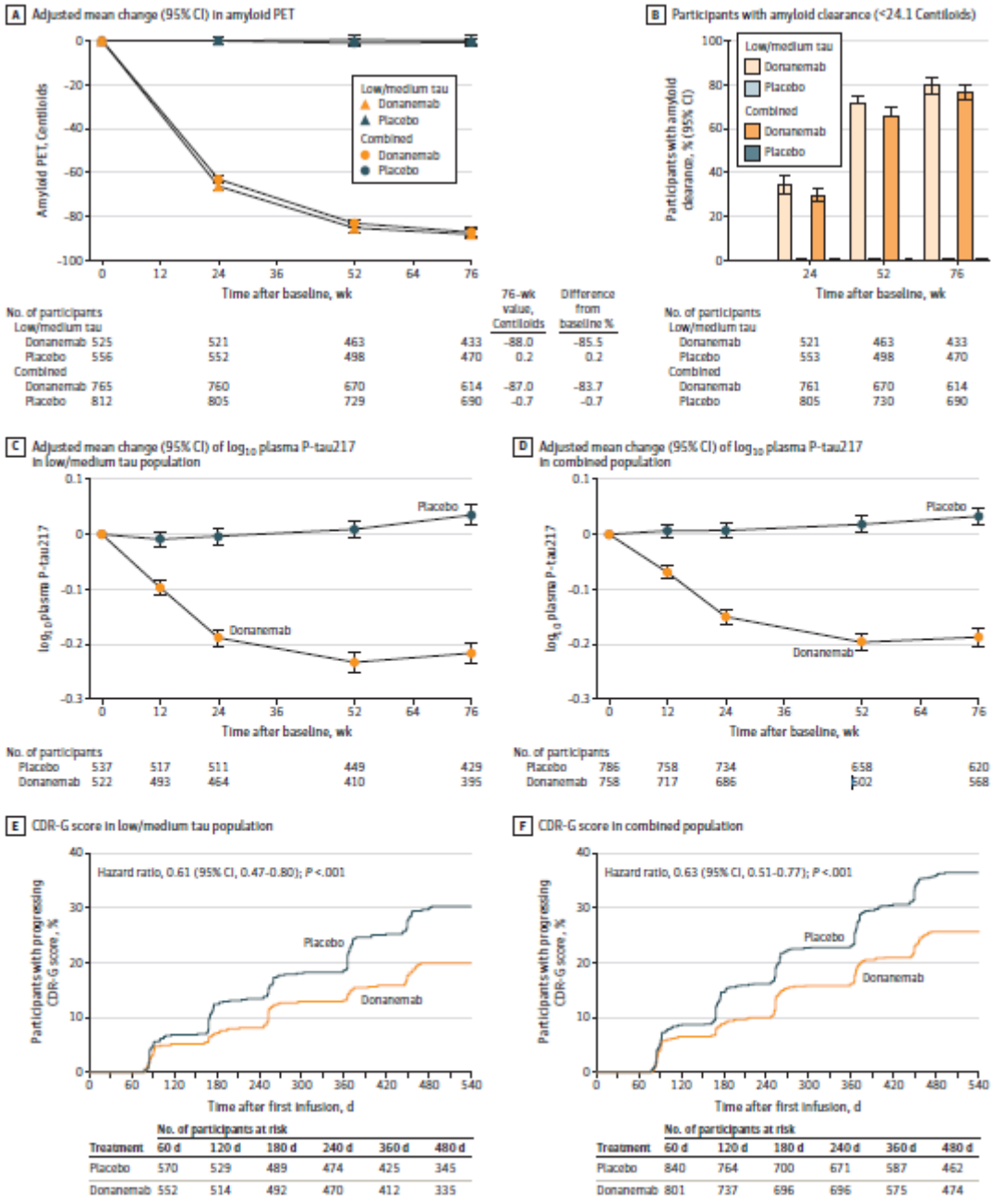
Amyloid PET: At 76 weeks, brain amyloid plaque level decreased by 88.0 Centiloids (95% CI, −90.20 to −85.87) with donanemab treatment and increased by 0.2 Centiloids (95% CI, −1.91 to 2.26) in the placebo group in the low/medium tau population; in the combined population, amyloid plaque level decreased 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 (see figure 4.A). 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 (see figure 4B).

Plasma P-tau217: P-tau217 was significantly reduced from baseline with donanemab treatment compared with placebo in the low/medium tau and combined population. The difference in LSM change in tau SUVR (log10-based) vs placebo was −0.25 (95% CI, −0.28 to −0.22; P < .001) in the low/medium tau population and −0.22 (95% CI −0.24 to −0.20; P < .001) in the combined population at 76 weeks (Figure 4C and 4D).

Time-Based Analyses: There was a 38.6% (CDR-G hazard ratio, 0.61 [95% CI, 0.47- 0.80]; P < .001) lower risk of disease progression in the low/medium tau population and a 37.4% (CDR-G hazard ratio, 0.63 [95% CI, 0.51-0.77; P < .001) lower risk of disease progression in the combined population with donanemab treatment compared with placebo over the 18-month trial (CDR-G: Clinical Dementia Rating Global Score) (Figure 4, E and F).

Figure 4. Brain amyloid, plasma phosphorylated tau 217 (P-tau217), and hazard ratios for risk of disease progression



Biomarker data shown were analyzed 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.

Author's 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.

AMYLOID-PET IN NON-PHARMACOLOGICAL INTERVENTIONS.

1. FINGER study in at-risk elderly people (Ngandu T. et al., 2015).

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER study) was a proof-of-concept randomised controlled trial aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population.

In a double-blind randomised controlled trial, individuals aged 60–77 years were recruited from previous national surveys. **Inclusion criteria** were CAIDE (Cardiovascular Risk Factors, Aging and dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age (score based on age, sex, education, systolic blood pressure, body-mass index [BMI], total cholesterol, and physical activity; range 0–15 points). Cognitive screening was done with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, and participants had to meet at least one of the following criteria: word list memory task (ten words three times) results of 19 words or fewer; word list recall of 75% or less; or mini mental state examination of 26 points or less out of 30 points. **Exclusion criteria** were previously diagnosed dementia; suspected dementia after clinical assessment by study physician at screening visit (individuals recommended for further investigations); mini mental state examination less than 20 points; disorders affecting safe engagement in the intervention (e.g., malignant disease, major depression, symptomatic cardiovascular disease, revascularisation within 1 year previously); severe loss of vision, hearing, or communicative ability; disorders preventing cooperation as judged by the study physician; and coincident participation in another intervention trial.

Randomly, 1260 participants were assigned in a 1:1 ratio to a 2-year multidomain intervention (n=631, diet, exercise, cognitive training, vascular risk monitoring), or a control group (n=629, general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation.

The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score. A thorough cognitive assessment with standard neuropsychological tests (an extended version of the neuropsychological test battery [NTB]) was done at baseline and at 12 and 24 months after randomisation by study psychologists. Cognitive decline was defined as any decline compared with improvement or no decline on the NTB total score (overall decline) and NTB domain Z scores (decline per domain). Other secondary outcomes included vascular and lifestyle factors, depressive symptoms (Zung scale), and disability (short physical performance battery).

RESULTS: 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total Z score at 2 years was 0·20 (SE 0·01, SD 0·51) in the intervention group and 0·16 (0·01, 0·51) in the control group. The mean difference between groups (group × time interaction) in change of NTB total score per year was 0·022 (95%CI 0·002–0·042, p=0·030). Improvement in NTB total score after 24 months was 25% higher in the intervention group than in the control group. The results remained unchanged in sensitivity analyses, including intention-to treat analyses.

Author's conclusion: Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

2. MAPT study in elderly adults with memory complaints (Andrieu S. et al., 2017).

The Multidomain Alzheimer Preventive Trial (MAPT study) was a 3-year, multicentre, randomised, placebo-controlled superiority trial with four parallel groups at 13 memory centres in France and Monaco. The study was aimed to investigate the effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention (physical activity, cognitive training, and nutritional advice), alone or in combination, compared with placebo, on cognitive function in elderly adults with memory complaints.

Participants were non-demented, aged 70 years or older, and community-dwelling, and **met at least one of three criteria**: spontaneous memory complaint expressed to their physician, limitation in one instrumental activity of daily living, or slow gait speed (≤0· 8 m/s, or more than 5 s to walk 4 m). Participants with a Mini Mental State Examination (MMSE) score lower than 24, those in whom dementia was diagnosed, and those with any difficulty in basic activities of daily living **were excluded**, as were those taking polyunsaturated fatty acid supplements at baseline.

They were randomly assigned (1:1:1:1) to either the multidomain intervention (43 group sessions integrating cognitive training, physical activity, and nutrition, and three preventive consultations) plus omega 3 polyunsaturated fatty acids (i.e., two capsules a day providing a total daily dose of 800 mg docosahexaenoic acid, DHA, and 225 mg eicosapentaenoic acid, EPA), the multidomain intervention plus placebo, omega 3 polyunsaturated fatty acids alone, or placebo alone. A computer-generated randomisation procedure was used to stratify patients by centre. All participants and study staff were blinded to polyunsaturated fatty acid or placebo assignment, but were unblinded to the multidomain intervention component. Assessment of cognitive outcomes was done by independent neuropsychologists blinded to group assignment.

The primary efficacy outcome was change from baseline to 36 months in a composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test, ten MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale—Revised, and the Category Naming Test [i.e., 2 min category fluency in animals]). The primary outcome was modified through a protocol amendment from one cognitive test to a composite cognitive score, which is now thought to be a better endpoint. Two different word lists were used at alternating visits for the Free and Cued Selective Reminding Test, to avoid learning effects. For all other tests or sub-tests, the same version was used at each visit.

All clinical and functional outcomes were assessed at baseline and at 6, 12, 24, and 36 months. Amyloid PET scans were done at five sites either at baseline or during follow-up (up to 36 months). Regional 18F-florbetapir standardised uptake volume ratios were obtained via semi-automated quantitative analysis, in which the cerebellum was the reference region. All adverse events and concomitant diseases and medications were recorded at 6, 12, 18, 24, 30, and 36 month follow-up visits during a consultation with a physician that included a physical examination. Blood sample analysis was also done at 6, 12, 24, and 36 months. Death and any other reasons for premature discontinuation of follow-up were recorded during follow-up and reported on a special form.

Additionally to the primary efficacy analysis, a post-hoc subgroup analyses were also done according to APOE ε4 genotype, and the presence of brain amyloid deposition, in a subsample of the population who underwent a florbetapir (18F) PET scan, which was judged to be positive when standardised uptake value was 1·17 or greater.

RESULTS: 1680 participants were enrolled and randomly allocated between May 30, 2008, and Feb 24, 2011. In the modified intention-to-treat population (n=1525), there were no significant differences in 3-year cognitive decline between any of the three intervention groups and the placebo group. Between-group differences compared with placebo were 0·093 (95% CI 0·001 to

0·184; adjusted p=0·142) for the combined intervention group, 0·079 (–0·012 to 0·170; 0·179) for the multidomain intervention plus placebo group, and 0·011 (–0·081 to 0·103; 0·812) for the omega 3 polyunsaturated fatty acids group. 146 (36%) participants in the multidomain plus polyunsaturated fatty acids group, 142 (34%) in the multidomain plus placebo group, 134 (33%) in the polyunsaturated fatty acids group, and 133 (32%) in the placebo group had at least one serious emerging adverse event. Four treatment related deaths were recorded (two in the multidomain plus placebo group and two in the placebo group). The interventions did not raise any safety concerns and there were no differences between groups in serious or other adverse events.

Author's conclusion: The multidomain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over 3 years in elderly people with memory complaints. An effective multidomain intervention strategy to prevent or delay cognitive impairment and the target population remain to be determined, particularly in real-world settings.

In the additional post-hoc subgroup analyses done according to the presence of brain amyloid in a subsample of 269 participants with amyloid PET scans, less cognitive decline during follow-up was noted in the combined intervention group (adjusted p<0·0001) and in the multidomain intervention plus placebo group (p=0·003) than in the placebo group in amyloid-positive participants.

2.4.1. Discussion on clinical efficacy

Based on published literature, the MAH is seeking the approval of a new indication for Neuraceq PET to "monitor the biological treatment response to pharmacological and non-pharmacological interventions".

According to the submitted literature, the claimed extension of indication might be divided into two parts:

a) monitoring of the biological treatment response to pharmacological interventions and,

b) monitoring of the biological treatment response to non-pharmacological interventions.

Data submitted for non-pharmacological interventions setting were based on two clinical trials to test the effect of multidomain intervention arms versus placebo/control arm. The FINGER study evaluated the effect of a multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring) versus control (general health advice). The MNAT study assessed the effect of physical activity, cognitive training, and nutritional advice or omega 3 polyunsaturated fatty acid supplementation against placebo. In both studies, the population included was at risk of cognitive decline or memory complaints and is broader than population where PET with Neuraceq is indicated, (i.e, adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment). Moreover, no efficacy data with florbetaben (18F) PET have been presented in these studies. The scientific rationale justifying the use of amyloid PET in monitoring of not-amyloid targeted treatment effects has not been provided. Consequently, the submitted data does not support the use of florbetaben (18F) in the patients on non-pharmaceutical interventions is not supported.

The most relevant studies with Neuraceq PET for pharmacological therapy monitoring are the Phase 3 studies GRADUATE I and II studies (Bateman et al., 2023), CLARITY AD study (van Dyck et al., 2022) and TRAILBLAZER-ALZ 2 study (Sims et al., 2023). These studies evaluated efficacy of amyloid-lowering drugs against placebo using clinical scores. PET with Neuraceq and other approved radiopharmaceuticals were used to monitor longitudinal changes on β-amyloid burden in patients treated with these therapies. Consistently, a clear decreased uptake in PET images is

shown in the β-amyloid-lowering therapy arm versus placebo when PET is used to monitor the reduction of β-amyloid.

In the studies **GRADUATE I and II (Bateman et al., 2023)**, some substudies that involved longitudinal cerebrospinal fluid (CSF) evaluation for amyloid, PET evaluation for amyloid, or PET evaluation for tau were conducted to evaluate the effect of gantenerumab on brain amyloid and tau levels.

In one of these substudies, the amyloid level was assessed with florbetaben (18F) or flutemetamol (18F) PET, but results were not presented individually, therefore, it is not possible to extract separated conclusions for Neuraceq. However, evidence supports that amyloid level on PET among participants receiving gantenerumab was lower than the level among those receiving placebo. The study does not present data on correlation between PET, biomarkers and the gantenerumab level reached in CSF. The conclusion was that the use of gantenerumab aimed to lower amyloid plaque was not associated with slower clinical decline. In these studies, amyloid-negative status was set at an amyloid level ≤24 centiloids. No correlation between β--amyloid reduction in the treatment arm monitored with PET and clinical response can be concluded.

In the **CLARITY AD study (Van Dyck et al., 2022)**, efficacy of lecanemab against placebo in patients with early AD was evaluated. Amyloid PET was assessed indistinctly with the three Fluorine-18 radiopharmaceuticals approved in the EU, therefore, no clear conclusions can be retrieved for Neuraceq. In this regard, it is unclear to which extent the observed changes on PET can be generalised across various radiopharmaceuticals. 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. In this study, the threshold for amyloid positivity was set at approximately 30 centiloids. Other biomarkers have been assessed but no data have been reported in the publication. Similarly to the study by Bateman et al., 2023, correlation analysis against other diagnostic tests measuring amyloid and response to treatment has not been discussed.

TRAILBLAZER-ALZ 2 study (Sims et al., 2023). In this study, donanemab significantly slowed Alzheimer disease progression, based on the iADRS score, compared with placebo in the low/medium tau and combined tau populations and across secondary clinical outcomes of CDR-SB, ADASCog13, and ADCS-iADL scores. Similarly than previous studies, amyloid pathology was assessed with 18F-florbetapir or 18F-florbetaben positron emission tomography (PET), and presence of tau pathology assessed by 18F-flortaucipir PET imaging with central image evaluation. Amiloid clearance was set at <24.1 Centiloids.

In summary, the clinical data available in the published literature as submitted by the MAH show a consistent uptake pattern in PET, decreasing in patients under amyloid-lowering treatment whereas uptake is not affected or slightly increases in the placebo arm. However, the evidence submitted by the MAH has important limitations.

According to the Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1,) clinical benefit of a diagnostic agent should be demonstrated by assessing its technical performance, diagnostic performance and by an appropriate discussion on the impact on diagnostic thinking and patient management. It is recognized that diagnostic performance (sensitivity and specificity) was established at the time of the Marketing Authorisation (MA) for Neuraceq considering histopathology from autopsy as standard of truth. In the clinical setting where the indication is claimed, it is agreed that direct measurement of amyloid is not feasible, therefore, there is not a standard of truth to establish the true level of β-amyloid. In this regard, correlation analysis between biomarkers and clinical parameters to inform about changes in beta-amyloid

might be useful to provide a very good approximation to the true disease state. However, in the data submitted by the MAH, correlation between reduction of β--amyloid level monitored with PET, clinical outcome and other biomarkers is not conclusive.

The MAH further discussed the studies presented in the initial MA to demonstrate the ability of Neuraceq PET to detect amyloid burden in the approved diagnostic setting (pivotal phase 3 study and retrospective study to support quantification as adjunct to visual read). Moreover, the MAH discussed the ability of amyloid PET to detect changes in amyloid burden due to natural accumulation, in patients receiving amyloid-targeting therapies (ATT) and the correlation of these changes with clinical outcomes and other biomarkers. However, extrapolation of efficacy for diagnostic performance to the monitoring setting showing that technical performance (inter- intra-reader variability) is similar in patients receiving ATT versus baseline images (repeated PET in the same patient) with the approved image interpretation criteria has not been demonstrated. Thus, a proper reader study should be conducted to support the extension of indication.

One of the most important aspects in this clinical setting is to demonstrate adequate technical performance, mainly test-retest reliability in the same patient, at baseline scan and in follow-up scans. Inter- and intra-reader variability needs also be studied. In this regard, the approved methodology for images interpretation with Neuraceq is the visual reading. The use of quantitative information as an adjunct to visual assessment is also approved according to the instructions stated in the SmPC of Neuraceq. In the literature submitted by the MAH, criteria for image interpretation have not been established. The MAH has been asked to discuss the role of different factors on the variability in repeated quantitative measurements. These factors include use of different PET devices and software, inter- and intra-reader variability, impact of amyloid-targeting treatments on the uptake of florbetaben (18F) (e.g., due to competitive binding at the target location, disturbed distribution to the target location). The threshold for definition of 'change'/'response' should be validated. If such methodology has not yet been established, it should be developed and validated.

During the assessment of the application, the MAH presented a test-retest variability of 4.6% for 18F-florbetaben PET based on the Villamagne et al., 2011 study. However this value is not acceptable as test-retest variability calculation was carried out with different formulations of Neuraceq.

Test-retest variability for different amyloid PET tracers (11C-PIB, and Fluorine-18 radiopharmaceuticals) presented by the MAH can only be considered as exploratory as no proper reader studies have been carried out.

The MAH also discussed the reliability and robustness of the Centiloid metric. The MAH refers to the recent CHMP qualification opinion (EMA DOC-1700519818-1200791) for Centiloid Unit as a validated, robust and reliable measurement for the quantification and monitoring of amyloid levels. The MAH claimed that Centiloid is a validated and appropriate tool to measure amyloid changes in different scenarios, including monitoring amyloid levels in patients treated with amyloid-lowering drugs, or when undergoing other pharmacological or non-pharmacological interventions. However, it should be noted that the context of use of this CHMP qualification opinion is "for the measurement of brain amyloid burden in subjects with early or established Alzheimer's disease pathology to be used in clinical trials. The Centiloid Unit can be used as adjunct to visual reads (negative with white matter retention only, positive with cortical tracer retention) with different tracers and PET scanning and analysis procedures…… Use of the Centiloid Unit as prognostic or predictive measure is currently not in scope of the Context of Use". In this regard, at time of the MAA, a longitudinal study to evaluate the relationship between florbetaben (18F) imaging and

changes in diagnostic status (from MCI to AD) was carried out by the MAH. However, the design of this study did not allow estimating the risk of MCI progression to clinical AD.

CHMP conclusion on the above qualification opinion was that the Centiloid Unit for the measurement of brain amyloid level can be considered a validated measure of global amyloid load in the brain for enrichment in clinical studies, if properly used with quality control procedures. The advantage would be potential use of different PET tracers and scanning and analysis procedures (scanning pipelines) in cross sectional settings, as non-normalised raw data for different available tracers are not comparable. Therefore, Centiloid Unit enables comparison between different PET radiopharmaceuticals and pipelines but interpretation criteria in clinical practice with Neuraceq, as stated in the approved SmPC, must be followed. Moreover, "the use of the Centiloid scale can provide a potential baseline measure for future therapy monitoring/follow up scanning. However, the clinical utility would depend on the clinical data that need to be generated for the specific future therapy. Amyloid PET is only one of the tools used to monitor patients receiving therapies against AD, since it is still not uncontroversial if lowering beta amyloid actually translates into clinically relevant treatment effects and if yes, to which magnitude. Therefore, any use, e.g. for surrogacy of efficacy or monitoring treatment response, is currently premature".

It seems that MAH´s proposal is to use quantitative measurement (CL) instead of the approved visual image interpretation without additional data to justify this change. It should be noted that quantitative measurement was approved as adjunct to visual interpretation based on data analysed in a retrospective clinical study, which assessed the diagnostic performance of the quantitative assessment of florbetaben (18F) PET scans against the histopathological confirmation, and the concordance between visual majority read of five independent blinded readers and quantitative assessment of florbetaben (18F) PET scans.

Altogether, the MAH should discuss how the use of Centiloid Unit in clinical practice could be used instead of visual image interpretation in the claimed indication. Then, the MAH should discuss and provide data to support the extension of indication, such as validated methodology for image interpretation and quantitative/semi-quantitative measurements (reference region, relevant regions of interest, minimum relevant threshold to define change, etc.). If such methodology has not yet been established, it should be developed and validated. Role and place of approved visual interpretation with a dual outcome (negative/positive) should be considered. Methodology and thresholds in Centiloid Units to define relevant changes should be defined and included in the SmPC.

The approved imaging interpretation criteria (visual read and quantification as adjunct to visual read) is proposed by the MAH for monitoring the β-amyloid plaque density to amyloid-targeting therapies. In the evidence presented by the MAH, it is noted that quantification (SUVr or centiloids) is the main methodology for imaging interpretation. The clinical use and adequacy of quantification to monitor subtle changes in patients receiving amyloid-targeting therapies is recognized, but methodology for imaging interpretation in the clinical setting for monitoring should be presented and validated.

Finally, clinical utility by assessing the impact on patient management has not been demonstrated by the MAH for the claimed indication. The CHMP adopted recently a positive opinion for lecanemab recommending the granting of a MA for the treatment of early AD. In this clinical setting, where there is not a standard of truth, impact on patient management should be demonstrated. The MAH does not propose thresholds for Neuraceq PET to guide the management of patients receiving amyloid-targeting therapies. The MAH refers to the labelling of these ATTs for changing the patient management, which can be agreed, but technical performance for monitoring should be studied.

Likewise, generalisation on efficacy of Neuraceq PET in monitoring of treatment β-amyloid plaque density across various amyloid-targeting therapies has not been demonstrated. If these data are not available, a limitation on generalisation data across different ATT should be mentioned in the SmPC.

In conclusion, evidence submitted by the MAH to extrapolate diagnostic performance from the approved indication to monitoring is inadequate. Assessment on variability of minimally relevant change in radiopharmaceutical uptake, which would differentiate true changes in the amyloid burden versus test-retest variability has not been provided. Test-retest variability/reliability and technical performance of 18F-Florbetaben PET on repeated scans for monitoring the beta amyloid plaque in patients receiving ATT should be established. The MAH recommends authorised imaging methodology for monitoring of treatment effects of ATT with Neuraceq PET. However, the data presented relies mainly on quantitation (SUVr and centiloids) instead of visual read criteria. It is expected that quantitative measurements might be the standard approach for image evaluation, but imaging methodology should be established for monitoring.

A reader study according to the guideline on clinical evaluation of diagnostic agents and appendix 1 on imaging agents (several blinded, off-site, trained readers) should be proposed and conducted to address the following aspects:

a) Extrapolation of diagnostic performance from diagnostic to monitoring setting may be possible if inter- intra- reader variability of images in patients receiving ATT versus variability at baseline (repeated PET in the same patient) is similar and provided that the same image interpretation criteria that have been approved for Neuraceq are used.

Test-retest variability of images on treatment versus baseline images should be measured. Repeated PET scans, measured in SUVrs and centiloids, should be used.

Non-inferior reliability (intra-/inter-reader variability) should be tested, i.e, the reliability of the test on treatment should be similar to or non-inferior to the reliability at baseline. Analyses of images with Neuraceq PET in patients receiving ATT (and on placebo as a control, if available) and at baseline if available from previous studies may be considered. Otherwise, prospective data collection will be required.

b) Imaging interpretation criteria, including quantitative measurement method for definition of relevant change/minimally relevant change in response to ATT on Neuraceq PET, should be established and reflected in the SmPC. These criteria should consider the observed variabilities (test-retest and reader variability), and thresholds for quantitative measurements should be defined in SUVrs and centiloids.

2.4.2. Conclusions on the clinical efficacy

Data submitted by the MAH to support the efficacy of PET with Neuraceq for the monitoring of β-amyloid plaque density in the brain of adult patients receiving amyloid-targeting therapy are insufficient.

In response to the CHMP 2nd request for supplementary information, the MAH decided not to further pursue the extension of indication but proposed to finalise the procedure with the other acceptable Product Information update (section 4.5 and 5.1) and RMP changes (see section 2.6 Risk Management plan and section 2.7 Update of Product information).

2.5. Clinical safety

2.5.1. Discussion on clinical safety

The MAH did not discuss the clinical safety aspects for the proposed extension of indication with use of Neuraceq to monitor β-amyloid plaque density in the brain of adult patients receiving amyloid-targeting therapy.

Monitoring the β-amyloid plaque density might carry out a higher exposition to radiation than when PET with Neuraceq is used in the approved indication. Therefore, the CHMP is of the view that the increased radiological risk in the claimed indication should be discussed by the MAH and included in the SmPC.

2.5.2. Conclusions on clinical safety

Safety profile of Neuraceq is well known but in case of PET with Neuraceq were used with higher frequency in the claimed indication, the increased radiological risk should be discussed by the MAH and included in the SmPC.

In response to the CHMP 2nd request for supplementary information, the MAH decided not to further pursue the extension of indication but proposed to finalise the procedure with the other acceptable Product Information update (section 4.5 and 5.1) and RMP changes (see section 2.6 Risk Management plan and section 2.7 Update of Product information).

Therefore, following the change of scope, the safety profile of Neuraceq remains unchanged.

2.6. Risk management plan

The MAH decided to not pursue the initially requested extension of indication.

The MAH submitted an updated RMP version 7.0 with this application, with removal of the additional risk minimisation measure in the form of educational materials as recommended by PRAC.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 7.0 with the following content:

Safety concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Not applicable

2.7. Update of the Product information

As a result of the extension of indication assessment, the MAH decided not to further pursue the extension of indication but proposed to finalise the procedure with the other Product Information update.

The MAH proposed the following updates of the Product Information:

- update section 4.5 of the SmPC to reflect new preclinical data and editorial change in section 5.1.

- Package leaflet update with discontinuation of the paper copy SmPC.

In addition, in line with the agreed RMP, Annex IID is updated with deletion of additional risk minimisation measures

The above proposed changed are considered acceptable by the CHMP.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

3. Benefit-Risk Balance

3.1. Favourable effects

Data submitted from literature envisage that PET with florbetaben (18F) is able to detect changes in amyloid level in patients treated with drugs based on amyloid-targeting antibodies.

3.2. Uncertainties and limitations about favourable effects

The evidence submitted by the MAH has several limitations:

- Adequate diagnostic information that PET with Neuraceq is able to reflect true changes in amyloid levels in patients receiving amyloid-targeting therapies (ATT) has not been provided. Extrapolation of efficacy (diagnostic performance) from diagnostic to monitoring setting showing that technical performance (inter- intra- reader variability) in test-retest (repeated PET in the same patient) is similar in patients receiving ATT versus at baseline images has not been demonstrated. Technical performance (i.e., test/re-test in the same patient, inter- and intra-reader variability) for the claimed indication has not been presented. Thus, a proper reader study should be conducted to extrapolate diagnostic performance from diagnostic to monitoring setting.

- Methodology for imaging interpretation in the clinical setting for monitoring has not been presented and validated.

- Generalisation of diagnostic efficacy of Neuraceq PET across various amyloid-targeting products is not established.

3.3. Unfavourable effects

Repeated exposition with Neuraceq PET can result in an increased risk to radiation, which should be reflected in the SmPC as relevant.

3.4. Benefit-risk assessment and discussion

3.4.1. Importance of favourable and unfavourable effects

Monitoring the β-amyloid plaque density with Neuraceq PET in patients treated with amyloid-targeting treatments could represent an outstanding benefit for patient management.

The higher exposition to radiation in this new clinical setting compared to the approved indication would be acceptable if adequately addressed in the labelling of the product.

3.4.2. Balance of benefits and risks

Although the risks are considered acceptable, the benefits for the claimed indication have not been established. Therefore, based on the assessment of the data contained in the application, the CHMP is of the view that the proposed extension of indication submitted under category C.I.6 of the variation classification Guideline could not be supported.

Following the CHMP assessment, the MAH decided not to pursue the extension of indication further but proposed to finalise the procedure with the other Product Information update (section 4.5 and 5.1) and RMP changes (see section 2.6 Risk Management plan and section 2.7 Update of Product information). The CHMP agreed that the updated proposed changes, as proposed by the MAH and falling under category C.I.4, are acceptable.

3.5. Conclusions

Based on the assessment of the data contained in this application, the CHMP concluded that the extension of indication for Neuraceq to include monitoring of the β-amyloid plaques in the brain of adult patients receiving ATT cannot be supported.

Following the MAH decision not to pursue the extension of indication, the CHMP agrees that the revised update of Product Information and RMP are acceptable. The overall B/R of Neuraceq remains positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) accepted		Type	Annexes affected
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II	I, II and IIIB

Update of section 4.5 of the SmPC to reflect new preclinical data and editorial update of section 5.1. The Package Leaflet is also updated with discontinuation of the paper copy SmPC. In addition, Annex IID is updated with deletion of additional risk minimisation measures. The RMP version 7.0 is agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated on for this variation.

In particular, the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to the Scientific Discussion for Neuraceq EMA/VR/0000227744.

Attachment

1. Product Information (changes highlighted) Neuraceq as adopted by the CHMP on 24 July 2025.