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The Preclinical Alzheimer Cognitive Composite:

Measuring Amyloid-Related Decline

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Study concept and design: Donohue, Sperling, Salmon, Raman, Aisen.
Acquisition, analysis, or interpretation of data: Donohue, Sperling, Rentz, Thomas, Weiner, Aisen.
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Abstract

IMPORTANCE—As Alzheimer disease (AD) research moves to intervene in presymptomatic phases of the disease, we must develop outcome measures sensitive to the earliest disease-related changes.

OBJECTIVE—To demonstrate the feasibility of a cognitive composite outcome for clinically normal elderly participants with evidence of AD pathology using the ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC). The ADCS-PACC combines tests that assess episodic memory, timed executive function, and global cognition. The ADCS-PACC is the primary outcome measure for the first clinical trial in preclinical AD (ie, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study).

DESIGN, SETTING, AND PARTICIPANTS—With the ADCS-PACC, we derive pilot estimates of amyloid-related decline using data from 2 observational studies conducted in North America and another conducted in Australia. The participants analyzed had normal cognition and mean ages of 75.81, 71.37, and 79.42 years across the 3 studies.

MAIN OUTCOMES AND MEASURES—For the 2 studies that collected data on Aβ levels (ADNI and AIBL), we estimate decline in a preclinical AD "Aβ-positive" placebo group and compare them with an "Aβ-negative" group. For the study that did not include data on Aβ levels (the ADCS Prevention Instrument [ADCS-PI] study), we grouped participants by the presence of *APOE*-ε4 and by clinical progression.

RESULTS—In ADNI, Aβ-positive participants showed more decline than did Aβ-negative participants with regard to the ADCS-PACC score at 24 months (mean [SE] difference, −1.239 [0.522] [95% CI, −2.263 to −0.215]; $P = .02$). In AIBL, the mean (SE) difference is significant at both 18 months (−1.009 [0.406] [95% CI, −1.805 to −0.213]; $P = .01$) and 36 months (−1.404 [0.452] [95% CI, −2.290 to −0.519]; $P = .002$). In the ADCS-PI study, *APOE*-ε4 allele carriers performed significantly worse on the ADCS-PACC at 24 months (mean [SE] score, −0.742 [0.294] [95% CI, −1.318 to −0.165]; $P = .01$) and 36 months (−1.531 [0.469] [95% CI, −2.450 to −0.612]; $P = .001$). In the ADCS-PI study, cognitively normal participants who progress from a global Clinical Dementia Rating score of 0 are significantly worse on the ADCS-PACC than cognitively normal participants who are stable with a global Clinical Dementia Rating score of 0 at months 12, 24, and 36 (mean [SE] ADCS-PACC score, −4.471 [0.702] [95% CI, −5.848 to −3.094]; $P < .001$). Using pilot estimates of variance and assuming 500 participants per group with 30% attrition and a 5% α level, we project 80% power to detect effects in the range of $\Delta = 0.467$ to 0.733 on the ADCS-PACC.

CONCLUSIONS AND RELEVANCE—Analyses of at-risk cognitively normal populations suggest that we can reliably measure the first signs of cognitive decline with the ADCS-PACC. These analyses also suggest the feasibility of secondary prevention trials.

The field of Alzheimer disease (AD) research has evolved to conceptualize AD as a continuum of disease.[1–4] Although, historically, AD was considered to begin with the onset of dementia, a predementia stage, characterized clinically as mild cognitive impairment and, more specifically, using biomarkers, as prodromal AD, has been widely accepted.[5–7] Most recently, the preclinical stage of AD has been postulated. This asymptomatic stage, believed to precede mild cognitive impairment by years, is characterized by accumulating amyloid pathology and neurodegeneration accompanied by very subtle cognitive decline detectable with sensitive neuropsychological tests and cognitive complaint measures.[1] Individuals with preclinical AD (ie, cognitively normal individuals with biomarker evidence of brain amyloid deposition) represent a group at high risk for decline and an ideal population for a "secondary prevention" trial aimed at delaying the emergence of the clinical syndromes of mild cognitive impairment and dementia.[8]

Drug development strategies in very early stages of the AD process initially focused on biomarkers that might efficiently demonstrate change-occurring years before the onset of symptoms. Examples of such candidate biomarker outcomes have included volumetric magnetic resonance imaging,[9] positron emission tomography (PET) with[18] fluorodeoxyglucose,[10] amyloid PET imaging,[11,12] and cerebrospinal fluid (CSF) markers.[13] Although each of these proposed outcomes reflect disease progression, the impact of therapeutic interventions aimed at disease modification has been surprising. For example, antiamyloid immunotherapy may paradoxically accelerate brain atrophy as measured by volumetric magnetic resonance imaging.[14] Until a reliable surrogate biomarker is validated, the field must rely on clinical outcome measures that reflect cognitive function.

Studies have shown that cognitive performance, measured using tests ranging from the Mini-Mental State Examination (MMSE) to word list learning tasks, may also show changes many years before the onset of functional decline.[2,15,16] Cognitive measures have important advantages over imaging and biochemical biomarkers: they are closely related to the core symptoms of disease progression and, at later stages, are sensitive to treatment effects. The US Food and Drug Administration has recently indicated support for the potential utility of cognitive composite measures as outcome measures in AD trials conducted at the preclinical stage.[17]

We describe a composite cognitive performance measure, the Alzheimer Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC). The ADCS-PACC is designed to serve as the primary outcome measure for trials conducted at the asymptomatic phase of AD. We describe, in particular, how the ADCS-PACC will be implemented in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study (hereafter referred to as the A4 study), which is being conducted by the ADCS in partnership with Eli Lilly.[18]

Methods

The A4 Study Design

The A4 study will be a 168-week placebo-controlled "secondary prevention" trial of an anti-Aβ treatment, aimed at slowing cognitive decline in cognitively normal older individuals

who have elevated brain amyloid levels (ie, “Aβ-positive” individuals), based on florbetapir PET amyloid imaging.[18] The A4 study will include a natural history arm of “Aβ-negative” cognitively normal individuals followed up with longitudinal cognitive outcome measures collected at the same intervals. There are also 2 embedded substudies: (1) an ethics protocol to investigate the impact of disclosure of Aβ status and (2) a novel outcome instrument development protocol to optimize the detection of early decline over the course of preclinical AD.

Eligible participants will be 65 to 85 years of age at the time of screening, with a global Clinical Dementia Rating (CDR-G) score of 0, an MMSE score of 27 to 30, and a Delayed Recall score on the Logical Memory IIa subtest of 8 to 15 for participants with 13 or more years of education, or with an MMSE score of 25 to 30 and a Delayed Recall score on the Logical Memory IIa subtest of 6 to 13 for participants with 12 or less years of education. A study goal is to include approximately 20% of participants from underrepresented minority groups.

The antiamyloid intervention for the A4 study is solanezumab, a monoclonal antibody targeting the midsequence of monomeric Aβ; this treatment was selected by the consensus of a panel of experts advising the A4 study team. A total of 1000 Aβ-positive participants will be randomly assigned to solanezumab or placebo. Identifying these Aβ-positive participants will require screening approximately 3000 cognitively normal older individuals by use of florbetapir PET amyloid imaging. This screening process will provide an opportunity to collect plasma biomarkers and imaging and neuropsychological data on a large number of Aβ-negative individuals representing a well-characterized “gold standard” cognitively normal control group.

The ADCS-PACC

The primary objective of the A4 study is to test the hypothesis that solanezumab, administered as a 400-mg intravenous infusion every 4 weeks for 168 weeks, will slow cognitive decline compared with placebo in participants with preclinical AD. This objective will be assessed using a mixed model of repeated measures (MMRM) analysis of change in the ADCS-PACC score. The specific hypothesis of the A4 study is that there will be less of a decrease in the ADCS-PACC score at the end of the treatment period for participants treated with solanezumab than for participants treated with placebo.

Based on a review of the literature for cohort studies in “normal controls” who progressed to mild cognitive impairment or Alzheimer dementia, we determined that a composite measure sensitive to change in preclinical AD would likely require assessment of 3 key domains: episodic memory, executive function, and orientation. Previous studies[19–21] have reported evidence that both list learning and paragraph recall (measures of episodic memory) tend to decline 7 to 10 years prior to the diagnosis of MCI or Alzheimer dementia. Recent data from amyloid imaging studies[25–29] have reported a decline in multiple cognitive domains looking retrospectively at cognitive trajectories over 8 to 10 years prior to PET amyloid imaging[22–24] and prospectively over 1- to 3-year longitudinal follow-up.

Based on this review, we propose a composite of 4 measures that are well established as showing sensitivity to decline in prodromal and mild dementia, and with sufficient range to detect early decline in the preclinical stages of the disease. The ADCS-PACC includes:

1. The Total Recall score from the Free and Cued Selective Reminding Test (FCSRT) (0–48 words),[20,30]
2. The Delayed Recall score on the Logical Memory IIa sub-test from the Wechsler Memory Scale (0–25 story units),[31]
3. The Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale–Revised (0–93 symbols),[32] and
4. The MMSE total score (0–30 points).[33]

The composite score is determined from its components using an established normalization method.[34] Each of the 4 component change scores is divided by the baseline sample standard deviation of that component, to form standardized z scores. These z scores are summed to form the composite. Thus, a change of 1 baseline standard deviation on each component would correspond to a 4-point change on the composite. In the A4 study, the ADCS-PACC will be administered at baseline and at 24, 48, 72, 96, 120, 144, and 168 weeks, alternating between 3 test versions.

Sensitivity of the ADCS-PACC

The ideal outcome measure for the A4 study is one that is sensitive to decline that is specific to the Aβ-positive cognitively normal target population, as opposed to decline that is associated with aging. To estimate the rate of Aβ-mediated decline and inform the sample size justification for the A4 study, we examined several natural history data sets. With each data set, a group similar to the A4 study cognitively normal Aβ-positive target population is identified and compared longitudinally with a reference cognitively normal Aβ-negative population. Estimated group differences provide an upper bound on potential treatment effects in our target population. We also explore group differences between those who maintain a CDR-G score of 0 (“CDR-G stable”) vs those who progress from a CDR-G score of 0 to a worse score (“CDR-G pro-gressor”). These progression group differences provide a sense of the clinical interpretation of the composite.

Data Sets and Measures

AD Neuroimaging—The Alzheimer’s Disease Neuroimaging Initiative (ADNI) has followed up with volunteers who were cognitively normal or who had varying degrees of cognitive impairment since 2005.[35] The ADNI battery includes serial neuroimaging, CSF measures, other biomarkers, and clinical and neuropsychological assessments. For the present analysis, we analyze the subset of cognitively normal participants from the initial wave of ADNI with known CSF Aβ42 levels or Pittsburgh compound B (PiB) PET images. We classify these cognitively normal participants as Aβ-positive participants, with a PiB standardized uptake value ratio (SUVR) above 1.5 and a CSF Aβ42 level below 192 pg/mL, or as Aβ-negative participants, with a PiB SUVR below 1.5 and a CSF Aβ42 level above

192 pg/mL. If only 1 of the 2 Aβ measures is known, we use that measure for classification. Data were obtained from the ADNI database on June 7, 2013.

The ADNI battery does not include the FCSRT. In place of the FCRST, we use Delayed Word Recall from the Alzheimer's Disease Assessment Scale–Cognitive Subscale[36] to construct an approximation of the proposed ADCS-PACC. To more closely reflect the inclusion criteria for the A4 study, we exclude ADNI participants with Delayed Recall scores greater than 15 on the Logical Memory IIa subtest.

Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing—The Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing (AIBL) is a longitudinal biomarker cohort study,[37] similar to ADNI. We used the same PiB threshold to determine Aβ positivity (PiB SUVR > 1.5). The AIBL battery also does not include the FCSRT, so we use delayed recall from List A of the California Verbal Learning Test[38] to construct the composite in the analysis of AIBL data.

ADCS Prevention Instrument Study—The ADCS Prevention Instrument (ADCS-PI)study was a 4-year study of cognitively normal individuals 75 years of age or older to assess potential outcome measures for future prevention studies.[16,30] The ADCS-PI study used New York University Paragraphs,[39] instead of Logical Memory, and the Modified Mini-Mental State Examination,[40] instead of the MMSE. The study data do not include CSF or PET measures of amyloid level. Therefore, as a proxy for Aβ status, we use the presence of at least 1 *APOE*-ε4 allele, although this is less predictive of decline than Aβ markers.[26] We also compare participants who were CDR-G stable with those who were CDR-G progressors. This last group definition is based on post baseline progression data and is bound to demonstrate larger group differences than the other analyses based on baseline covariates only. However, this analysis of postbaseline progression puts the scale of the composite in perspective relative to clinically meaningful CDR-G change.

The ADNI, ADCS-PI, and AIBL studies were all approved by the institutional review boards of all of the participating institutions. Informed written consent was obtained from all participants at each site.

Sample Size Justification for the A4 Study

For each of the data sets and group comparisons already described, we apply an MMRM to estimate the key variance and covariance parameters that inform sample size calculations. The model includes effects for baseline ADCS-PACC score and age, which is known to be associated with Aβ accumulation in brain. The MMRM treats time as a categorical variable and estimates group differences at each visit while making no assumptions about the shape of trajectories. We use the Akaike information criterion[41] to select the covariance structure between unstructured, compound symmetric, and autoregressive correlations of the order 1. From the final model, we report the difference between the at-risk population and the reference population at the final visit, which is typically the test statistic of primary interest in a clinical trial. We also report *P* values with an adjustment for simultaneous inference[42] and area between the curves using the trapezoid rule.[43] Power calculations assume an MMRM to estimate treatment effect at 36 months, 6-month visit intervals, 500 participants

per group, 30% attrition, and a 5% α level. We use the formula by Lu et al[44] implemented in the R package longpower[45] to project the smallest detectable effect. The formula accommodates general attrition patterns. We assume that attrition accumulates linearly to an overall 30% attrition rate at 3 years with 5% worse attrition in the active arm. We report minimum detectable effects on the raw scale (eg, ADCS-PACC units) and as a percentage of the mean decline in the at-risk group (eg, Aβ-positive individuals, *APOE*-ε4 carriers, or CDR-G progressors). All analyses are conducted using R version 3.0.1[46] and the nlme[47] and longpower[45] packages. Graphics are produced using the ggplot2 package.[48]

Optimized Item Weights

We explored optimized reweighting of the ADCS-PACC components (see eAppendix in the Supplement for results). We fit Item Response Theory models[49] to a training set composed of ADNI cognitively normal participants with unknown Aβ status to optimize the ADCS-PACC and also search for other items that might improve performance. We also reweighted the ADCS-PACC item z scores based on a logistic regression of AIBL Aβ statusand a Nelder-Mead optimization[50] of MMRM power in terms of minimized detectable percentage of Aβ group difference. We also assessed the power of CDR Sum of Boxes and each of the ADCS-PACC items.

Results

Baseline Characteristics

Table 1 and Table 2 summarize baseline characteristics for each of the groups analyzed. In ADNI and AIBL, we see that the Aβ-positive groups are significantly older at baseline and have significantly higher percentages of *APOE*-ε4 carriers compared with the Aβ-negative groups. Not surprisingly in ADNI, the Aβ-positive groups also show significantly lower CSF Aβ42 levels, higher T-tau levels, higher PiB SUVRs, and smaller hippocampi than do the Aβ-negative groups. In AIBL, the Aβ-positive group shows more impairment on Digit Symbol Coding than does the Aβ-negative group. In the ADCS-PI study, the CDR-G progressor group demonstrated greater baseline impairment on the FCSRT and Modified Mini-Mental State Examination than did the CDR-G stable group, and the *APOE*-ε4 carriers were younger than the noncarriers.

Longitudinal Analysis of the ADCS-PACC

The Figure, Table 3, and Table 4 summarize the change in the ADCS-PACC scores over time as estimated by the MMRM, controlling for baseline ADCS-PACC score and age. The Akaike information criterion selected the compound symmetric correlation over the other correlation structures considered. In ADNI, there was significant separation of the Aβ groups at 24 months but a reconvergence of the trajectories at 36 months. The mean (SE) area between the curves is −26.4 (13.6) ($P = .05$). In AIBL, we see consistent significant separation at both month 18 and month 36 and area between curves. In the ADCS-PI study CDR-G stable vs progressor analysis, we see highly significant ($P < .001$) separation at months 12, 24, and 36 and area between curves. In the ADCS-PI study *APOE*-ε4 carriers vs noncarriers analysis, we see significant separation at months 24 and 36 and significant area between the curves.

Minimum Detectable Treatment Effect on the ADCS-PACC

Based on the variance and correlation estimates in Tables 3 and 4, we can estimate the minimum treatment effect that can be found by assuming 80% to 90% power, a 5% α level (2-sided), 500 participants in each group, and 30% attrition. The Figure depicts the minimum detectable treatment effect for 80% power.

Using ADNI pilot estimates of variance and correlation (Table 3), we project a minimum treatment difference of Δ = 0.525 to 0.607 units for 80% to 90% power. This is larger than the observed Aβ group difference in ADNI at month 36 but is 0.525/1.239 = 42.4% to 0.607/1.239 = 49.0% of that difference at month 24. Similarly, using the AIBL pilot estimates (Table 3), we project Δ = 0.467 to 0.540 units, or 0.467/1.404 = 33.3% to 0.540/1.404 = 38.5% of the Aβ group difference at month 36. Based on estimates from the analysis of ADCS-PI study CDR-G stable vs progressor groups (Table 4), we project Δ = 0.654 to 0.746 units, or 0.654/4.471 = 14.6% to 0.746/4.471 = 16.7% of the group difference at month 36. Based on the analysis of ADCS-PI study *APOE*-ε4 carriers vs noncarriers (Table 4), we project Δ = 0.733 to 0.847 units, or 0.733/1.531 = 47.9% to 0.847/1.531 = 55.3% of the month 36 group difference. Again, the Figure graphically represents these smallest detectable treatment effects.

Discussion

Our analyses demonstrate consistent evidence that Aβ-positive cognitively normal participants demonstrate greater cognitive decline than do Aβ-negative participants on a composite of verbal list learning, paragraph recall, timed executive function, and global cognition. Moreover, we found that decline on this composite was robust across cohorts, regardless of the exact measures used;however, in ADNI, we did not see significant changes from baseline, and the amyloid group difference was only significant at month 24. The inconsistencies between the various studies used in our retrospective analysis also present some limitations. The particular tests that comprised each study's entire battery, and their order of presentation, varied from study to study. In addition, none of the studies analyzed were treatment trials. Owing to these factors, the ADCS-PACC may behave differently in the A4 study.

These limitations not with standing, we project that the A4 study has about 80% power to detect a treatment benefit of 0.5 ADCS-PACC units over 3 years. A quarter standard deviation change in each component of the ADCS-PACC equates to a1-point change in the ADCS-PACC total score. The ADCS-PACC is standardized according to the baseline distribution of 4 instruments with established face validity in more impaired populations. We believe 0.5 ADCS-PACC units is small enough to be a realistically attainable, yet large enough to suggest benefit to patients, including a reduction in later clinical deterioration.

The Item Response Theory approach applied to ADCS-PACC items did not improve power in ADNI, although a model with 16 items did achieve more consistent decline and Aβ group separation in ADNI (eFigure and eTable in the Supplement). The logistic regression approach decreased the smallest detectable effect (percentage of Aβ group difference) at 80% power by 6.5% when applied to same AIBL data that were used to obtain the weights.

The weighting favored list and paragraph recall over MMSE and Digit Symbol Substitution. However, when these weights were applied to the other studies, it performed poorly. The smallest possible effect size was only 1.5% smaller than the logistic regression weights, and this required weighting Digit Symbol Substitution in the wrong direction. We have concerns about the validity of optimized weighting, particularly given that there is no information about treatment response for these items in the target population. It is conceivable, for example, that we would down-weight a particular item that would respond to treatment, but we have no information with which to assess this risk. At this point, we do not find strong evidence to support unequal weighting of the ADCS-PACC items.

Ideally, the A4 study would be powered to detect a clinically meaningful effect. The term *clinically meaningful effect* is somewhat nebulous but presumably indicates an effect on symptoms of importance to the treated individual. In a 3-year study in the clinically normal target population for the A4 study, we will not necessarily observe the emergence of functional impairment seen in late mild cognitive impairment and dementia. However, because a composite measure of memory, orientation, and executive function has face validity as an indicator of AD-related clinical progression, the recent US Food and Drug Administration draft guidance[17,51] suggests that such a measure may serve as a primary outcome measure for the purpose of accelerated approval, with clinical meaningfulness supported by postmarketing study.

The A4 study will include a number of secondary and exploratory measures to inform interpretation of the treatment effect on the primary measure. These include molecular, structural, and functional neuroimaging measures, CSF biochemical markers, and patient- and informant-reported measures of perceived global and specific cognitive function. Experience with such measures in longitudinal studies in the preclinical AD population is limited, and their sensitivity to treatment effects is unknown. However, they may clarify not only the pathophysiological impact of the antiamyloid intervention but also the implications of the cognitive effects.

Conclusions

The concept of preclinical AD, a stage of amyloid-mediated neurodegeneration before the emergence of clinical symptoms,[1,8] represents an attractive target for disease-modifying intervention in AD. The relationship of longitudinal change in the ADCS-PACC to the presence of amyloid plaques in the brains of asymptomatic older individuals supports the notion that this measure may be useful in establishing favorable treatment effects. While much remains to be learned about preclinical AD, the enormity of the need for effective therapy requires the rapid initiation of trials. Presumably, the A4 study and other very early interventional studies will further elucidate the trajectory of cognitive decline during the preclinical stages of AD and facilitate the successful development of disease-modifying treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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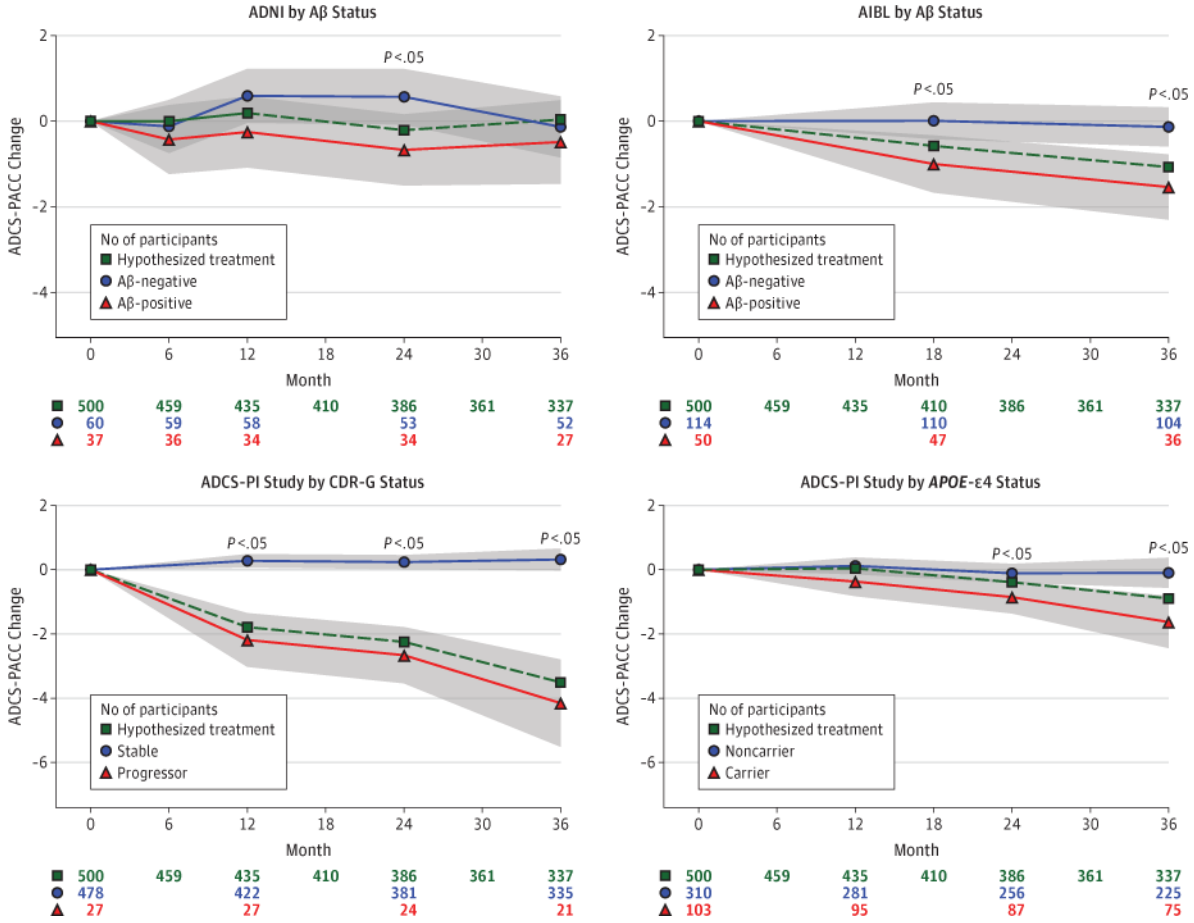

Figure. MMRM Estimates of Composite Change From Baseline in the ADCS-PACC

The models assume heterogeneous compound symmetric covariance structure, which allows for a different variance per visit and for a single correlation parameter. Age and composite score at baseline are included as covariates. The dashed line indicates the hypothesized minimum treatment benefit that can be detected with 80% power, a 5% α level, and the indicated sample size and attrition. The shaded regions depict 95% CIs. Group differences are significant at $P < .05$. ADCS-PACC indicates Alzheimer's Disease Cooperative Study Preclinical Alzheimer Cognitive Composite; AIBL, Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; CDR-G, global Clinical Dementia Rating; MMRM, mixed model of repeated measures; and PI, Prevention Instrument.

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Table 1

Baseline Characteristics of Participants in ADNI and AIBL, by Aβ Status[a]

Characteristic	Participants With Available Data, No.	Aβ-Negative Participants	Aβ-Positive Participants	All	*P* Value[b]
ADNI					
Total No.		60	37	97	
Age, y	97	74.80 (5.43)	77.45 (4.74)	75.81 (5.31)	.006
Female sex	97	30 (50)	12 (32)	42 (43)	.09
Education, y	97	15.17 (2.91)	15.46 (3.22)	15.28 (3.02)	.49
APOE-ε4 alleles	97				
0		53 (88)	20 (54)	73 (75)	<.001
1		7 (12)	16 (43)	23 (24)	
2		0 (0)	1 (3)	1 (1)	
Word List Delayed Recall score	97	3.02 (1.65)	3.24 (1.64)	3.10 (1.64)	.48
Logical Memory Delayed Recall score	97	11.10 (2.56)	11.35 (2.68)	11.20 (2.59)	.62
MMSE score	97	28.83 (1.15)	29.05 (1.05)	28.92 (1.11)	.33
Digit Symbol Substitution Test score	97	45.60 (9.27)	42.30 (8.49)	44.34 (9.08)	.09
ADAS-Cog score	97	9.96 (3.81)	11.13 (4.12)	10.41 (3.95)	.12
CSFAβ42 level, pg/mL	90	244.3 (27.2)	144.9 (26.3)	206.8 (55.4)	<.001
CSF T-tau level, pg/mL	90	61.2 (19.8)	82.2 (35.8)	69.2 (28.7)	.005
PiB SUVR	15	1.244 (0.101)	1.900 (0.122)	1.594 (0.356)	<.001
FDG uptake, average intensity score	52	6.500 (0.607)	6.327 (0.703)	6.430 (0.646)	.38
CDR-SB score of 0.5	97	5 (8)	1 (3)	6 (6)	.26
UCSF hippocampi, %ICV ×1000	87	485.7 (62.1)	459.4 (50.0)	476.3 (59.1)	.04
UCSF ventricles, %ICV ×1000	87	1989 (980)	2387 (878)	2131 (959)	.02
AIBL					
Total No.		114	50	164	
Age, y	164	69.75 (6.83)	75.06 (6.91)	71.37 (7.26)	<.001
Female sex	164	61 (54)	26 (52)	87 (53)	.86
Education, y	164	12.51 (2.53)	12.27 (2.70)	12.44 (2.58)	.49

Characteristic	Participants With Available Data, No.	Aβ-Negative Participants	Aβ-Positive Participants	All	*P* Value[b]
APOE-ε4 alleles	164				
0		77 (68)	17 (34)	94 (57)	<.001
1		34 (30)	31 (62)	65 (40)	
2		3 (3)	2 (4)	5 (3)	
Word List Delayed Recall score	164	11.95 (2.97)	11.82 (3.16)	11.91 (3.02)	.88
Logical Memory Delayed Recall score	162	11.87 (3.75)	10.88 (4.14)	11.57 (3.89)	.12
MMSE score	164	28.89 (1.20)	28.68 (1.17)	28.83 (1.19)	.20
Digit Symbol Substitution Test score	164	59.7 (13.2)	55.5 (12.9)	58.5 (13.2)	.05

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; FDG,^{18} fluorodeoxyglucose; MMSE, Mini-Mental State Examination; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio; UCSF, University of California, San Francisco; %ICV, percentage of intracranial volume.

[a] All values are given as mean (SD) values or number (%) of participants, unless otherwise indicated.

[b] Determined by use of the Wilcoxon test for continuous variables and the Pearson χ^2 test for categorical variables.

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Table 2

Baseline Characteristics of Participants in the ADCS-PI Study, by Group[a]

Characteristic	Participants With Available Data, No.	Group of Participants			
		CDR-G Stable (n = 478)	CDR-G Progressor (n = 27)	All (n = 505)	*P* Value[b]
Age, y	505	79.36 (3.60)	80.52 (3.82)	79.42 (3.62)	.08
Female sex	505	286 (60)	19 (70)	305 (60)	.28
Education, y	505	15.05 (2.95)	14.15 (3.46)	15.00 (2.98)	.18
APOE-ε4 alleles	305				
0		223 (77)	13 (76)	236 (77)	.93
1		63 (22)	4 (24)	67 (22)	
2		2 (1)	0 (0)	2 (1)	
FCSRT Total Free Recall score	504	28.97 (5.53)	25.37 (5.99)	28.77 (5.61)	.01
FCSRT Total Recall score	504	47.851 (0.464)	47.556 (0.847)	47.835 (0.495)	.005
3MSE score	505	95.86 (3.37)	92.04 (4.10)	95.66 (3.51)	<.001
CDR-SB score of 0.5	505	90 (19)	8 (30)	98 (19)	.17
Digit Symbol Substitution Test score	495	42.1 (11.8)	34.2 (10.5)	41.7 (11.9)	<.001
NYU Paragraph Recall score	497	7.45 (2.80)	5.44 (2.39)	7.34 (2.81)	<.001
		***APOE*-ε4 Noncarrier (n = 310)**	***APOE*-ε4 Carrier (n = 103)**	**All (n = 413)**	
Age, y	413	79.73 (3.63)	78.58 (3.15)	79.44 (3.55)	.002
Female sex	413	170 (55)	59 (57)	229 (55)	.67
Education, y	413	14.94 (3.33)	15.38 (2.76)	15.05 (3.20)	.43
APOE-ε4 alleles	413				
0		310 (100%)	0 (0%)	310 (75%)	<.001
1		0 (0)	99 (96)	99 (24)	
2		0 (0)	4 (4)	4 (1)	
FCSRT Total Free Recall score	412	27.99 (6.01)	28.92 (5.71)	28.22 (5.94)	.06
FCSRT Total Recall score	412	47.803 (0.554)	47.853 (0.515)	47.816 (0.545)	.24
CDR-SB score	413	0.332 (0.507)	0.403 (0.560)	0.350 (0.521)	.28

Characteristic	Participants With Available Data, No.	Group of Participants		All (n = 505)	*P* Value[b]
		CDR-G Stable (n = 478)	CDR-G Progressor (n = 27)		
3MSE score	413	95.20 (3.88)	95.85 (3.15)	95.37 (3.72)	.27
Digit Symbol Substitution Test score	411	40.7 (12.1)	40.4 (11.9)	40.6 (12.0)	.79
NYU Paragraph Recall score	413	7.14 (2.82)	7.23 (2.72)	7.16 (2.80)	.65

Abbreviations: ADCS-PI, Alzheimer's Disease Cooperative Study Prevention Instrument; CDR-G progressor, global Clinical Dementia Rating score from 0 to worse score; CDR-G stable, global CDR score of 0; CDR-SB, Clinical Dementia Rating–Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; NYU, New York University; 3MSE, Modified Mini-Mental State Examination.

[a] All values are given as mean (SD) values or number (%) of participants, unless otherwise indicated.

[b] Determined by use of the Wilcoxon test for continuous variables and the Pearson χ^2 test for categorical variables.

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Table 3

MMRM Estimates of Composite Change From Baseline, by Study[a]

Month	Group	Participants, No.	Estimate (SE)	*P* Value	Adjusted *P* Value[b]	95% CI	σ Value[c]	ρ Value[d]
ADNI Aβ$^+$ (n = 36)vs Aβ$^-$ (n = 59)								
6	Aβ$^-$	59	−0.133 (0.310)	.67		−0.740 to 0.473		
	Aβ$^+$	36	−0.439 (0.401)	.28		−1.225 to 0.348		
	Difference		−0.306 (0.503)	.54	.94	−1.291 to 0.679	2.327	
12	Aβ$^-$	58	0.581 (0.315)	.07		−0.037 to 1.199		
	Aβ$^+$	34	−0.263 (0.414)	.53		−1.075 to 0.549		
	Difference		−0.844 (0.516)	.10	.30	−1.857 to 0.168	2.358	
24	Aβ$^-$	53	0.558 (0.325)	.09		−0.080 to 1.196		
	Aβ$^+$	34	−0.681 (0.415)	.10		−1.494 to 0.132		
	Difference		−1.239 (0.522)	.02	.06	−2.263 to −0.215	2.361	
36	Aβ$^-$	52	−0.145 (0.356)	.68		−0.843 to 0.553		
	Aβ$^+$	27	−0.497 (0.487)	.31		−1.451 to 0.457		
	Difference		−0.352 (0.599)	.56	.94	−1.527 to 0.823	2.578	0.459
Area between curves			−26.4 (13.6)	.05				
AIBL Aβ$^+$ (n = 47) vs Aβ$^-$ (n = 110)								
18	Aβ$^-$	110	0.009 (0.215)	.97		−0.412 to 0.429		
	Aβ$^+$	47	−1.000 (0.334)	.003		−1.655 to −0.345		
	Difference		−1.009 (0.406)	.01	.02	−1.805 to −0.213	2.213	
36	Aβ$^-$	104	−0.134 (0.229)	.56		−0.583 to 0.315		
	Aβ$^+$	36	−1.538 (0.381)	<.001		−2.285 to −0.791		
	Difference		−1.404 (0.452)	.002	.004	−2.290 to −0.519	2.315	0.520
Area between curves			−30.8 (10.1)	.002				

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; MMRM, mixed model of repeated measures; $^+$, positive;

– , negative.

[a] The models assume heterogeneous compound symmetric covariance structure, which allows different variance parameters (σ) per visit, and a single correlation parameter (ρ).

[b] Adjusted for model-based simultaneous inference.

[c] Residual standard deviation estimate at each visit.

[d] Estimated correlation between visits.

Table 4

MMRM Estimates of Composite Change From Baseline, by ADCS-PI Study Group[a]

Month	Group	Participants, No.	Estimate (SE)	*P* Value	Adjusted *P* Value[b]	95% CI	σ Value[c]	ρ Value[d]
CDR-G Progressor (n = 27) vs Stable(n = 422)								
12	Progressor	27	−2.187 (0.418)	<.001		−3.006 to −1.367		
	Stable	422	0.276 (0.105)	.009		0.070–0.482		
	Difference		−2.463 (0.435)	<.001	<.001	−3.316 to −1.610	2.121	
24	Progressor	24	−2.661 (0.438)	<.001		−3.519 to −1.804		
	Stable	381	0.238 (0.109)	.03		0.024–0.453		
	Difference		−2.899 (0.455)	<.001	<.001	−3.791 to −2.008	3.208	
36	Progressor	21	−4.153 (0.679)	<.001		−5.484 to −2.823		
	Stable	335	0.318 (0.170)	.06		−0.015 to 0.651		
	Difference		−4.471 (0.702)	<.001	<.001	−5.848 to −3.094	2.133	0.542
Area between curves			−91.2 (12.4)	<.001				
***APOE*-ε4 Carrier (n = 95) vs Noncarrier (n = 281)**								
12	Carrier	95	−0.370 (0.227)	.10		−0.815 to 0.075		
	Noncarrier	281	0.117 (0.131)	.37		−0.140 to 0.374		
	Difference		−0.487 (0.263)	.06	.16	−1.003 to 0.028	2.197	
24	Carrier	87	−0.854 (0.254)	.001		−1.352 to −0.356		
	Noncarrier	256	−0.112 (0.147)	.45		−0.400 to 0.176		
	Difference		−0.742 (0.294)	.01	.03	−1.318 to −0.165	3.646	
36	Carrier	75	−1.628 (0.406)	<.001		−2.423 to −0.833		
	Noncarrier	225	−0.098 (0.234)	.68		−0.557 to 0.362		
	Difference		−1.531 (0.469)	.001	.003	−2.450 to −0.612	2.388	0.547
Area between curves			−23.9 (7.84)	.002				

Abbreviations: ADCS-PI, Alzheimer's Disease Cooperative Study Prevention Instrument; CDR-G progressor, global Clinical Dementia Rating score from 0 to worse score; CDR-G stable, global CDR score of 0; MMRM, mixed model of repeated measures.

[a] The models assume heterogeneous compound symmetric covariance structure, which allows different variance parameters (σ) per visit, and a single correlation parameter (ρ).

[b] Adjusted for model-based simultaneous inference.

[c] Residual standard deviation estimate at each visit.

[d] Estimated correlation between visits.