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Original Article

Validation of a novel cognitive-functional outcome measure optimized for early Alzheimer's Disease: Evidence from the VIVA-MIND trial

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ABSTRACT

Background: Cognitive-functional composite measures are increasingly used as primary efficacy endpoints in early Alzheimer's disease (AD) trials, where greater sensitivity to decline can improve trial efficiency and reduce sample size requirements.
Objectives: To compare sensitivity to decline of the Cognitive Functional Component 2 (CFC2), a novel cognitive-functional composite measure described by Raghavan et al. (2013), against the Clinical Dementia Rating - Sum of Boxes (CDR-SB) and other standard cognitive and functional outcomes including MMSE, FAQ, ADAS Cog 13 and ADCOMS using prospective randomized clinical trial data.
Design: The VIVA-MIND trial was a phase 2A/2B randomized controlled trial investigating the safety and efficacy of varoglutamstat in patients with mild cognitive impairment and mild dementia due to AD.
Setting: The VIVA-MIND trial was conducted between 2021–2024. It was prematurely terminated in mid-2024 by the study sponsor.
Participants: This secondary analysis uses data from 98 participants in the modified intention-to-treat population from the VIVA-MIND trial with complete neuropsychological test data.
Measurements: Standard power calculations informed by parameters estimated from linear mixed-effects models were used to determine the relative efficiency of outcome measures.
Results: The CFC2 was more sensitive to decline than the CDR-SB in this population. Use of the CFC2 would yield a 15% reduction in required sample size relative to the CDR-SB. Application of an optimal weighting scheme further improved the sensitivity of the CFC2.
Conclusions: Practically significant differences in the efficiency of clinical trials in early AD may be realized by the choice of clinical outcome measure and weighting scheme. Although further verification is needed, we replicate a previous finding that the CFC2 may outperform the CDR-SB in the early AD population.

1. Introduction

Hybrid composite cognitive-functional measures are increasingly used as primary efficacy endpoints in clinical trials of treatments targeting early Alzheimer's disease (AD). These composites may have better measurement properties and enable trials with smaller sample size compared to trials using co-primary endpoints. More efficient endpoints allow trials to be performed at decreased cost, with less drain on the finite number of persons available to participate in clinical trials, and less human subject burden. Importantly, in contemporary clinical trials of disease-modifying anti-amyloid monoclonal antibody therapies enrolling participants with mild cognitive impairment (MCI) and mild

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AD dementia, composite cognitive-functional measures have been successfully used to demonstrate treatment efficacy [1–3]. These measures also comply with draft guidance from the Food and Drug Administration (FDA) that states that trials in Stage 3 early AD can use a single primary outcome measure if such a measure adequately and meaningfully assesses independent effects on both cognition and daily function. Here, Stage 3 early AD refers to persons with biomarker evidence of AD pathophysiological changes as well as apparent cognitive abnormalities and with mild functional impairment present but not rising to the level that would support a diagnosis of overt dementia [4,5]. Similarly, the European Medicines Agency (EMA) has acknowledged that composite measures capturing both cognitive and functional changes may be acceptable in this population. Consistent with this position, recent EMA marketing authorizations for disease-modifying AD therapies have been based on demonstrated efficacy on composite cognitive-functional measures [6,7]. In addition, regulatory approvals in other countries have been granted even in the absence of formal guidance specifying single or composite endpoints [8,9].

In the first draft guidance, published in 2013, the FDA endorsed the Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) as a suitable alternative to co-primary endpoints in early AD trials [10]. Since then, the CDR-SB has become a preferred primary efficacy endpoint in trials restricting to participants with Stage 3 early AD and in trials enrolling participants with either Stage 3 early AD or Stage 4 mild dementia due to AD. Examples include the EMERGE and ENGAGE trials of aducanumab [3], the Clarity AD trial of lecanemab [1], the GRADUATE I and II trials of gantenerumab [11], the HOPE4MCI trial of the drug AGB101 [12], and the ongoing CELIA phase 2 trial to evaluate the safety and efficacy the drug BIIB080 (NCT05399888). On the other hand, subsequent revisions of the guidance have refrained from endorsing a specific outcome measure in early AD and instead encouraged the development of novel approaches to the integrated evaluation of cognitive and functional impairment [4,5]. While the CDR-SB has been shown to have good psychometric properties [13–15] and to successfully quantify dementia severity and progression [16–19], its sensitivity to change in rate of decline relative to other composite cognitive-functional measures has not been rigorously evaluated in a prospective randomized clinical trial setting.

Composite measures are typically derived from assessment batteries used in observational longitudinal cohort studies. These data may or may not be representative of participants recruited to an active clinical trial [20]. To better inform the performance of novel cognitive outcomes in the clinical trial setting, they should be included as pre-planned secondary outcomes in an actual clinical trial. To this end the Cognitive Functional Component (CFC2) [21], a novel cognitive-functional composite described by Raghavan and colleagues [21], was included as the key secondary endpoint in the VIVA-MIND trial. The CFC2 is the sum of Word Recall, Delayed Word Recall, and Orientation from the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); box scores for the cognitive components of the CDR (Memory, Orientation, Judgement & Problem Solving); and the Functional Activities Questionnaire (FAQ). The range of the CFC2 is 0 to 67, with higher scores indicating greater impairment in global functioning. Using data from MCI and AD participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) longitudinal study, the CFC2 has been shown to be more sensitive to decline than the CDR-SB in this population [21]. While the CDR-SB was the primary efficacy endpoint for phase 2B of VIVA-MIND, inclusion of the CFC2 as a secondary outcome allows for comparison of the relative sensitivity of these measures using prospective clinical trial data. Other secondary and exploratory endpoints that were included in the VIVA-MIND trial served as additional benchmarks.

For composite outcome measures, additional gains in statistical power can be realized by applying an optimal composite weighting scheme [22]. Optimal weights for constructing a composite endpoint are a function of the expected change and covariance of change of the component tests and are intended to maximize the sensitivity to detect rate of decline. Using an optimal composite weighting scheme is an alternative to calculating composites by either summing the component scores, as in the CFC2, or by combining z-scores, as in the Neuropsychological Test Battery-7 (NTB-7) [23], the Preclinical Alzheimer's Cognitive Composite (PACC) [24], and the ADNI Battery Composite (ABC) [25]. The performance of optimal composite measures in the VIVA-MIND trial was explored using optimal weights for the CFC2 and the ABC that were independently derived from a representative sample in the ADNI database for the CFC2 and the ABC. Estimation of weights using the ADNI database ensures objective comparison of performance of the optimal composites with VIVA-MIND endpoints.

In summary, in this exploratory study we used the VIVA-MIND data to independently validate the use of a novel composite measure of cognition and everyday function in early AD. We compared the sensitivity of the CFC2 to change in cognitive decline vis-a-vis the CDR-SB to replicate the relative performance of these measures as reported by Raghavan et al. [21] and to extend these findings to a clinical trial setting. We similarly characterized the performance of a selection of other outcome measures collected in the VIVA-MIND trial. Throughout we reported standard power calculations in our comparison of all measures. For selected composite measures we additionally reported component measure weights derived from an independent longitudinal dataset (the ADNI cohort). Our goal through these analyses is to provide guidance in the selection of endpoints for clinical trials targeting early AD.

2. Methods

2.1. Data

The VIVA-MIND phase 2A/2B double-blind, placebo-controlled randomized trial investigated the safety and efficacy of varoglutamstat (PQ912), an oral small molecule glutaminyl cyclase inhibitor which reduces production of pyroglutamated Aβ and the inflammatory chemokine CCL2 (NCT03919162). Participants ($n = 112$) met clinical inclusion criteria for MCI or mild probable AD per NIA-AA guidelines [26,27], and had CSF biomarker criteria consistent with AD pathology [25]. Additional neuropsychological criteria at screening included a Mini-Mental State Examination (MMSE) score 20–30 [inclusive], a Montreal Cognitive Assessment (MoCA) score < 26, and a CDR global score of 0.5 or 1 (with memory component score > 0.5). In mid-2024, the VIVA-MIND trial was prematurely terminated by the study sponsor. Subsequent analyses indicated that none of the primary or secondary efficacy endpoints in VIVA-MIND were reached with the available study sample [28]. For this analysis we restricted to a subset of participants ($n = 98$) and visits with complete neuropsychological test data available for each of the measures of interest.

2.1.1. Outcome measures

The CDR-SB was the planned primary efficacy endpoint in phase 2B of the VIVA-MIND trial. The CFC2 was the key secondary efficacy endpoint in phase 2B and the ABC, the AD Assessment Scale - Cognitive Subscale (ADAS-Cog-13), and the Functional Activities Questionnaire (FAQ) were other secondary efficacy endpoints. Additional exploratory endpoints were the MMSE, the MoCA, the Alzheimer's Disease Composite Score (ADCOMS) [29], and the ADAS-Cog-Exec [30]. A description of each measure including the relevant score range is available in Supplementary Table 1. With the exception of the CDR-SB, MMSE, and MoCA, which were first conducted as part of the screening visit, all measures were assessed at baseline and subsequently during scheduled visits at either 12 week or 24 week intervals.

2.1.1.1. CFC2. The CFC2 was derived by Raghavan et al. [21] using data from the ADNI cohort. Raghavan et al. identified cognitive composites and cognitive-functional composites that showed improved

performance compared to an established benchmark cognitive composite (the ADAS-Cog 11) and the CDR-SB. To construct these novel composite measures they first identified component measures where the mean/standard deviation ratio (MSDR) of 2-year change from baseline for a MCI cohort exceeded 0.4 units of standardized change. These measures included the "ADAS-3″ (the sum of ADAS-Cog Word Recall, Delayed Word Recall, and Orientation components), Immediate Recall from the Auditory Verbal Learning Test (AVLT), the CDR-SB cognitive components and CDR-SB functional components, the MMSE, and the FAQ. Three novel cognitive composites were formed using combinations of the cognitive measures, and three novel cognitive-functional composites were formed from the latter by adding the FAQ. The most sensitive cognitive composite was the Cognitive Composite 2 (CC2) which consisted of ADAS-3 and the CDR-SB cognitive components. The most sensitive cognitive-functional composite was the CFC2 which combined the CC2 with the FAQ. While the results are compelling, they have not been independently validated through replication using prospective RCT data.

2.2. Statistical methods

2.2.1. Assessment of performance

Several metrics were used to compare the performance of the various outcome measures. In comparing different outcome measures, the most important indication of performance is the signal (rate of change) in proportion to the noise (variability in change) henceforth referred to as the signal-to-noise ratio. Measures that have a high signal-to-noise ratio and therefore require a lower number of participants per arm are the most sensitive to detecting change in rate of decline. For a linear mixed-effects model analysis with random slopes and intercepts, the signal-to-noise ratio is a function of both the number and interval of assessment and the coefficient of change and variance parameters from this model [31]. Standard power calculations have been derived for the linear mixed-effects model analysis [32–34] and implemented using the R package *longpower* [35]. We used this software to compute statistical power to detect a hypothesized 25 % treatment effect as a function of sample size assuming a 72-week trial with assessments every 24 weeks. A 25 % treatment effect is consistent with the comparisons of the sensitivity of the CFC2 vis-a-vis the CDR-SB by Raghavan et al. [21] and with the effect sizes observed in trials demonstrating efficacy of recently approved monoclonal antibody treatments [5,27]. Parameters required for these power calculations were estimated by fitting linear mixed-effects models [31] to the subset of the VIVA-MIND trial data for which complete neuropsychological test data was available for the outcome measures considered in this analysis. In addition to fixed and random effects for intercept and time, the linear mixed-effects models included fixed effects to adjust for the initial diagnosis of MCI due to AD or mild AD dementia, and for the study site at which the visit was conducted. A treatment variable was not included as there was no statistically significant difference between treatment groups in any of the cognitive and functional endpoints with the available study sample. That is, the treatment and placebo arms were pooled for this analysis. Similarly, APOE genotype and education effects on rate of decline also did not reach statistical significance in this sample from the VIVA-MIND trial data. To simplify presentation these variables were not included in statistical models estimating power calculation parameters. Bootstrap confidence intervals were computed for sample size projections to reflect variability in the estimated parameters obtained from the linear mixed-effects model.

2.2.2. Optimal composite evaluation

To fully utilize the outcome measure data generated by the VIVA-MIND trial, empirical characterization of the relative performance of all possible cognitive-functional composites were calculated using the trial data. Optimal weights for constructing a composite endpoint maximize the signal-to-noise ratio of the composite and therefore the statistical power of clinical trials that use them. We estimated optimal weights from ADNI cohort data for both the CFC2 [21], and the ABC [25]. The interval of data collection in ADNI did not provide an exact match to the VIVA-MIND clinical trial. Ideally, the measurement interval of the training data set used to estimate optimal weights should match the measurement interval of the clinical trial to which the optimal weights will be applied. The sampling interval most representative of the 72 week (i.e. 18 month) final visit of the VIVA-MIND trial was the ADNI month 24 visit and these data were used to compute the optimal weights for the CFC2 and ABC.

3. Results

The demographics and baseline cognitive scores of the 98 VIVA-MIND trial participants that were considered as part of the modified intention-to-treat (mITT) population and had complete neuropsychological test data for the outcomes of interest are shown in Table 1. Participants had a mean age of 71.5 (SD = 7.6) years; 52.0 % were female; 75.8 % were APOE e4 carriers, and the mean years of education was 15.6 (SD = 2.8). At the screening visit 62.2 % had a diagnosis of MCI due to AD and 37.8 % were diagnosed as mild probable AD. The baseline mean score on the CDR-SB was 3.2 (SD = 1.6) and the baseline mean score on the CFC2 was 28.7 (SD = 9.2). The subset of participants retained for the analysis did not meaningfully differ from the mITT population with respect to demographic characteristics, APOE e4 carrier status, or diagnosis. The mean score and standard deviation of all outcome measures by visit are shown in Supplementary Figure 2 and reported in Supplementary Table 2. The mean follow-up time was 306 days (SD = 178). Attrition by visit is reported in Supplementary Table 2.

3.1. Performance of CFC2

The coefficient of change and variance parameters were estimated for the CFC2 and CDR-SB and their respective cognitive and functional components by a linear mixed effects model as described in Section 2.3 (Table 2). The sample size that is reported in Table 2 is the number of participants per arm required for 80 % power to detect a 25 % change in rate of decline. Fig. 1 shows power as a function of sample size for all measures. The signal-to-noise ratio of the CFC2 exceeded that of the CDR-SB in this population. Relative to the CDR-SB, the CFC2 would require 15 % fewer participants to detect a treatment effect in a 72 week clinical trial. For the 25 % effect size powered here, this translates to $n = 46$ fewer participants per arm. Both cognitive-functional composites significantly outperformed all standard cognitive endpoints examined,

Table 1
Baseline characteristics of the subset of VIVA-MIND study participants with complete neuropsychological test data.

	Baseline ($n = 98$)
Age, mean (SD)	71.5 (7.6)
Female, n (%)	51 (52.0)
Race, n (%)	
White	93 (94.9)
Black or African American	5 (5.1)
Education, mean (SD)	15.6 (2.8)
APOE4 positive, n (%)	72 (75.8)
Initial diagnosis, n (%)	
MCI due to AD	61 (62.2)
Mild probable AD	47 (37.8)
CDR-SB, mean (SD)	3.2 (1.6)
CFC2, mean (SD)	28.7 (9.2)

Abbreviations: CDR-SB, Clinical Dementia Rating - Sum of Boxes; CFC2, Cognitive Function Component 2; SD, standard deviation. For the CDR-SB the best possible score is 0 and the worst possible score is 18. For the CFC2 the best possible score is 0 and the worst possible score is 67.

Table 2
Linear mixed effect model parameters and sensitivity to rate of change in a 72 week trial with assessments every 24 weeks.

Instrument	Fixed effect mean rate of change	Random slope SD (σ_β)	Residual error SD (σ_ϵ)	Signal-to-noise-ratio	N / arm (95 % CI) *	Relative Efficiency†
CDR-SB	1.23	1.11	0.85	0.90	314 (203,552)	1
CDR-SB-Cog	0.63	0.52	0.54	0.86	342 (208,610)	1.09
CDR-SB-Fun	0.59	0.61	0.50	0.76	441 (268,919)	1.41
CFC2	4.90	3.42	3.84	0.97	268 (169,538)	0.85
ABC	0.26	0.23	0.18	0.91	303 (180,542)	0.97
ADCOMS	0.15	0.12	0.09	1.00	251 (169,368)	0.80
MMSE	2.35	2.34	1.84	0.80	393 (230,782)	1.25
ADAS-Cog-13	2.68	3.70	3.79	0.51	952 (427,2910)	3.03
FAQ	3.11	3.20	2.68	0.75	442 (228,962)	1.41
Optimally weighted composites						
CFC2-OPT-WGT	1.27	0.88	0.91	1.02	243 (156,429)	0.77
ABC—OPT-WGT	1.16	0.65	0.92	1.06	226 (150,347)	0.72

*Projected sample size needed for 80 % power to detect a 25 % treatment effect assuming a 72-week trial with assessments every 24 weeks.
†Relative Efficiency = sample size: sample size of Clinical Dementia Rating - Sum of Boxes (CDR-SB). A relative efficiency of 0.80 means that a trial using the alternative measure would require 20 % fewer participants than a trial using CDR-SB.
Abbreviations: CDR-SB, Clinical Dementia Rating - Sum of Boxes; CDR-SB-Cog, Clinical Dementia Rating - Sum of Boxes cognitive components; CDR-SB-Fun, Clinical Dementia Rating - Sum of Boxes functional components; CFC2, Cognitive Function Component 2; ABC, ADNI Battery Composite; ADCOMS, Alzheimer's Disease Composite Score; MMSE, Mini-Mental State Examination; ADAS-Cog-13, Alzheimer's Disease Assessment Scale Cognitive, FAQ, Functional Activities Questionnaire; SD, standard deviation.

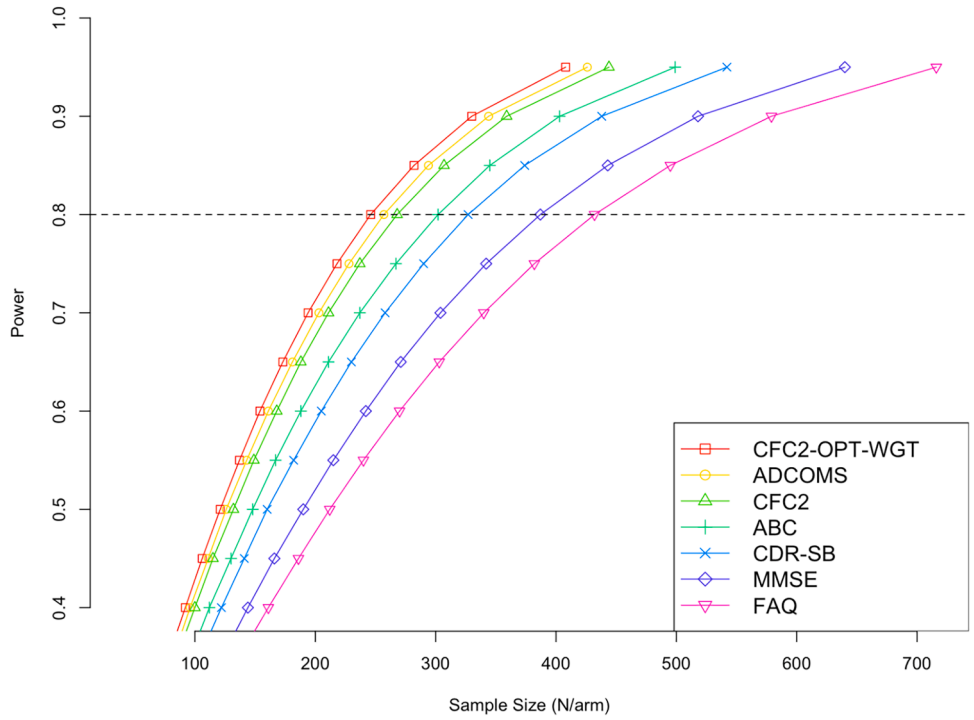

Fig. 1. Plots of power vs sample size requirement per treatment arm for trials with assessments at 24 week intervals, assuming a 25 % difference in rate of decline between treatment and control groups. Calculations are based on the parameters of a linear mixed effects model with random slopes fit to the subset of the VIVA-MIND data used in this analysis.
Abbreviations: CFC2, Cognitive Function Component 2; CFC2-OPT-WGT, optimally weighted CFC2; CDR-SB, Clinical Dementia Rating - Sum of Boxes; ABC, ADNI Battery Composite; ADCOMS, Alzheimer's Disease Composite Score; MMSE, Mini-Mental State Examination; FAQ, Functional Activities Questionnaire.

including the MMSE and the ADAS-Cog-13, as well as the FAQ functional endpoint.

3.2. *Performance of optimally weighted composite measures*

Optimal weights for the ABC and CFC2 (Supplementary Table 3) were estimated from an independent representative sample in ADNI as described in 2.2.2. The resulting optimally weighted composites significantly outperformed the composites computed using standard scoring. The optimally weighted CFC2 yielded a 9 % improvement in efficiency over the CFC2 and the optimally weighted ABC yielded a 25 % improvement in efficiency over the ABC. The optimally weighted CFC2 was the most sensitive cognitive-functional composite in this analysis, even yielding a 3.1 % improvement in efficacy over the ADCOMS which is a weighted sum based on partial least squares regression [29]. Use of the optimally weighted CFC2 would require $n = 71$ fewer participants per arm than the CDR-SB for the trial design indicated in this analysis, a 23 % improvement in efficiency.

4. Discussion

We showed that the CFC2 was more sensitive to change than the CDR-SB in early AD using prospective VIVA-MIND RCT data. Based on these analyses, use of the CFC2 would reduce the sample size required to detect a 25 % change in the rate of decline by 15 % compared to use of the CDR-SB. While the sensitivity of the CFC2 relative to the CDR-SB has previously been reported using observational cohort data from ADNI, the VIVA-MIND study provides important replication of this finding in a clinical trial setting. Notably, although cognitive measures (MMSE, CDR-SB cognitive components) were generally more responsive than functional measures (FAQ, CDR-SB functional components) in this early AD population, efficiency in this setting was optimized using composite cognitive-functional endpoints. This finding is consistent with prior evidence that measures of functional impairment capture distinct aspects of disease progression, even at early stages, thereby potentially improving composite endpoint performance while reflecting change across multiple clinically relevant domains affected in early AD.

An optimal composite weighting scheme using weights independently derived from a representative cohort in ADNI further improved sensitivity of the standard unweighted CFC2 by 9 %. The optimally-weighted CFC2 was the most sensitive cognitive-functional composite measure in this analysis, even slightly outperforming the ADCOMS cognitive-functional composite. These improvements in efficiency from using optimally weighted composite measures come at virtually no operational cost to the administration of a trial. However, the optimal weighting approach does require prior independent data from a representative sample to estimate weights. For the present study, the selected ADNI cohort was reasonably well matched to the VIVA-MIND study population with respect to initial diagnosis (69 % MCI and 31 % AD in ADNI compared to 62 % MCI and 38 % AD in VIVA-MIND), age (mean 74.5 years compared to 71.5), and APOE carrier status (71.8 positive compared to 75.8). On the other hand, with more trials making their data publicly available, the computation of weights based on large, representative cohorts is increasingly feasible through large data depositories.

We acknowledge several limitations to this study. The VIVA-MIND trial was terminated early, which resulted in lower-than-planned enrollment and number reaching the week 72 end-of-treatment visit. As a result, the sample size did not support analyses of all the secondary and exploratory outcomes collected in the trial, specifically the MoCA and the ADAS-Cog-Exec. The sample size also limited our study to power calculations based on a linear mixed-effects model while most contemporary clinical trials use mixed model for repeated measures (MMRM) or related analyses. Thus, the sample size projections reported here are not directly applicable to these analysis plans. However, our primary intention was to validate the use of the CFC2 as an endpoint in clinical trials of early AD by demonstrating that it is more sensitive to change in cognitive decline than the CDR-SB. We expect that our findings in this regard will generalize to trials in this population using the MMRM analysis plan, as the linear mixed-effects model is generally unbiased when the underlying trajectory is approximately linear [36] so that the relative efficiency of outcome measures under these two analyses plans is similar. Another limitation is that the CDR-SB and MMSE were administered at a screening visit and not at the baseline visit. In all post-baseline visits, instruments were administered together. The longer interval between the screening and post-baseline visits compared to the interval between the baseline and post-baseline visits means there was a slight bias in the estimated performance of the CDR-SB and MMSE towards greater sensitivity for detecting change. This may have also impacted the estimates of relative performance of composite measures derived from these tests, specifically the ADCOMS which incorporates the entire CDR-SB and components of the MMSE, and the performance of these measures may be modestly overestimated. As a sensitivity analysis, we repeated all calculations using change measured from week 24 to week 72 and found no substantial differences in relative efficiency from the findings reported here (Supplementary Table 4).

The VIVA-MIND trial provided a unique opportunity to validate the use of alternative hybrid cognitive-functional endpoints in a clinical trial setting. We demonstrated that within this Stage 3 and Stage 4 early clinical AD population the CFC2 is more sensitive than the CDR-SB in detecting differences in rate of decline. All cognitive-functional composite measures considered in this analysis outperformed standard cognitive and functional endpoints including the MMSE, the ADAS-Cog-13, and the FAQ. We also showed that optimal composite weighting offers substantial sample size savings over simple sum of score and use of z-score normed component weighting. The VIVA-MIND trial provides strong evidence that practically significant improvements in the efficiency of early AD trials may be realized by selecting a primary endpoint optimized to detect change in cognitive decline in the targeted clinical trial population, and further enhanced by the application of optimal weighting. However, responsiveness to change is only one consideration in endpoint selection. Statistically significant treatment effects are not necessarily clinically significant or meaningful without a clear understanding of what constitutes meaningful change on the selected measure [37]. Candidate outcome measures should therefore be evaluated based on the extent to which anticipated change signifies a clinical benefit to patients with AD and their families. Although benchmarks of meaningful change, including the minimally clinically important difference (MCID), have been established for each component measure of the CFC2 [38–41], such benchmarks have yet to be established for the composite itself. Moreover, the magnitude of the MCID may also change with the duration of treatment and disease stage [42]. Accordingly, further research will be needed to aid interpretation of statistically significant change on the CFC2 in terms of clinical benefit to patients and their families in early AD and within specific trial designs.

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Ethical statement

This study involved secondary analyses of data from the VIVA-MIND clinical trial (NCT03919162), a multicenter, randomized, placebo-controlled Phase 2b clinical trial conducted in participants with mild cognitive impairment or mild dementia due to Alzheimer's disease. The VIVA-MIND trial was conducted in accordance with the principles of the Declaration of Helsinki and International Council on Harmonization Good Clinical Practice guidelines. All trial participants provided written informed consent before data collection.

Data use statement

The ADCS Data and Sample Sharing Committee (DSSC) grants access to de-identified data to individuals who complete the request process and agree to the conditions in an ADCS/UCSD Data Use Agreement (DUA). After approval and receipt of the fully executed DUA, applicants are authorized to acquire data. Non-compliance with the DUA, including the requirement to provide requested updates will jeopardize further access to data.

Declaration of the use of generative AI and AI-assisted technologies

During the preparation of this work, the authors did not use any generative AI, AI-assisted technologies, or related tools.

CRediT authorship contribution statement

Jasmin A. Duehring: Writing – review & editing, Writing – original

draft, Methodology, Formal analysis. **Diane M. Jacobs:** Writing – review & editing, Methodology, Conceptualization. **David P. Salmon:** Writing – review & editing. **Andrew J. MacKelfresh:** Writing – review & editing, Data curation. **Carolyn Revta:** Writing – review & editing, Project administration. **Antje Meyer:** Writing – review & editing. **Michael Schaeffer:** Writing – review & editing. **Sylvia Schell-Mader:** Writing – review & editing. **Tanja Wassmann:** Writing – review & editing. **Christine Wenzkowski:** Writing – review & editing. **Howard H. Feldman:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Steven D. Edland:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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Supplementary materials

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