

Validation of a precision measure of cognitive change in a phase II clinical trial in early AD: The Early and Mild Alzheimer's Cognitive Composite (EMACC)

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Methodological Issue Being Addressed Commonly used measures of cognition in trials for early Alzheimer's disease (EAD) have significant limitations that negatively impact the ability to detect change and to understand the efficacy of novel therapies. Cognitive measures with higher precision produce more robust and replicable signals with smaller sample sizes and are greatly needed EAD.

Introduction The Early and Mild Alzheimer's Cognitive Composite (EMACC, Jaeger 2017) is an empirically derived composite of validated clinical neuropsychological tests statistically optimized for amyloid associated cognitive decline in early AD. Building on its development using multiple longitudinal aging cohorts, we report data from an ongoing phase two clinical trial that confirms feasibility and examines replicability and validation as compared to other endpoints.

Methods Data from an ongoing phase II, double-blind, placebo-controlled trial of early Alzheimer's disease sponsored by INmune Bio were used in these analyses (ClinicalTrials.gov ID NCT05318976). Screening and baseline data for the EMACC, CDR, and MMSE (screening only), were included in the analyses. The EMACC was computed by averaging the z-scores for 6 variables: Digit Symbol Coding, Trail-Making Test Parts A and B, Digit Span-Forward and Backward, Letter Fluency, Category Fluency, Verbal Learning (International Shopping List Task), using each test's baseline mean and standard deviation. Psychometric analyses include descriptive statistics to examine normality of distributions, Pearson correlations to evaluate test-retest reliability between screening and baseline visits and construct validity via associations with CDS-SB and MMSE. Paired-sample t-tests were used to evaluate practice effects between screening and baseline and ANOVA was used to estimate the difference on EMACC as a function of baseline CDR Global rating.

Results Screening and baseline data from 140 participants (48% Female), mean age of 73 years (SD = 6.47), meeting Alzheimer's disease diagnostic criteria at Jack stage 3 (MCI) or 4 (Mild AD) were available for this interim analysis. The EMACC score was normally distributed with no evidence of floor or ceiling effects. Statistically significant practice effects were evident on Digit Symbol-Coding, but not EMACC score. Mean duration between screening and baseline was 33 days (SD 10.7). Test-retest correlations for each EMACC component were medium to high (0.74 to 0.92), with an overall test-retest correlation of 0.93 for the EMACC score. Correlations between EMACC and CDR-SB and MMSE (at screening), were highly significant (both $p < .001$), and EMACC distinguished CDR Global Score levels of .5 vs. 1.0 (effect size=0.87, $p < .001$). Additional available

cases will be included in the final presentation.

Conclusion The EMACC is being successfully administered in a global clinical trial with high data integrity. Component measures demonstrate high levels of test-retest reliability from screening to baseline, with slight anticipated practice effects on one scale. The EMACC z-score composite shows high test-retest reliability and outstanding validity. There is a significant and clinically consistent relationship with overall dementia severity on CDR-SB. EMACC robustly distinguishes between CDR Global ratings of 0.5 and 1. Adoption of the EMACC has the potential to streamline clinical trials, reducing patient burden and sponsor cost while advancing development of new therapies by using precise and clinically meaningful cognitive measures in early AD.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

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