# ADCOMS Demonstrates Improved Sensitivity to Disease Progression and Treatment Effects in Early AD

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# Presentation Outline

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# Presentation Outline

- Why do we need a new tool?
- General approach to the task
- Development of ADCOMS as a clinical assessment outcome
- What can we learn from individual selected items?
- Sensitivity to decline and to treatment effects: ADCOMS versus existing clinical batteries
- Results from prospective studies
- Regulatory Support for New Sensitive Evidence-Based Clinical Outcomes in Early AD
- Conclusions

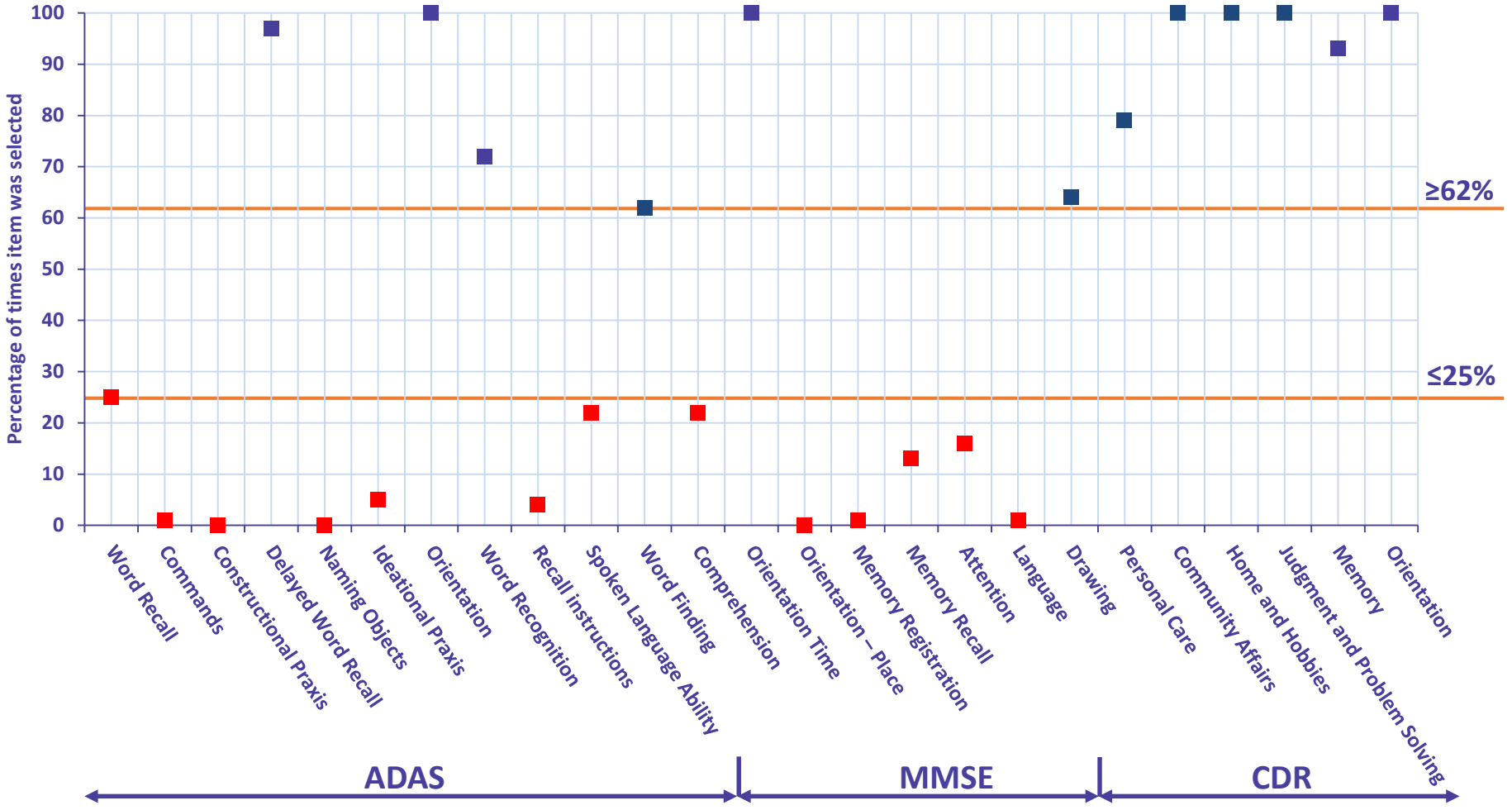
# Why do we need a new clinical assessment tool?

- Convergent effort within Alzheimer's disease (AD) field to target early stages of disease, such as mild cognitive impairment (MCI)
- AD community recognizes that no standard clinical endpoints exist that are sensitive to disease progression and treatment effect in MCI populations
- Significant burden for conducting trials in MCI → long and large trials, difficult to impossible to manage
- Not all is lost: there are select items in existing clinical scales that are relevant to an MCI population

# Methodology

- ***True clinical progression in MCI is represented by items that show***
  - *consistent decline across different MCI studies and*
  - *provide unique contributions*
- Partial Least Square (PLS) Regression Model
  - Fits a statistical model to pooled placebo data from 4 MCI studies over 1 year
  - Maximizes covariance between individual items and progression over time
  - Results in a better predictive model when there are numerous correlated individual items
- Use the model to select a linear combination of items from existing clinical tools (ADAS-Cog, MMSE, CDR-SB, NTB, …)
  - Combination most sensitive to decline → the new clinical tool
  - Items assigned weights by the PLS model to optimize sensitivity to decline

# Items Clearly Separated into Two Distinct Groups




**Reliability assessed using split sample validation (100 random training samples and test samples)**

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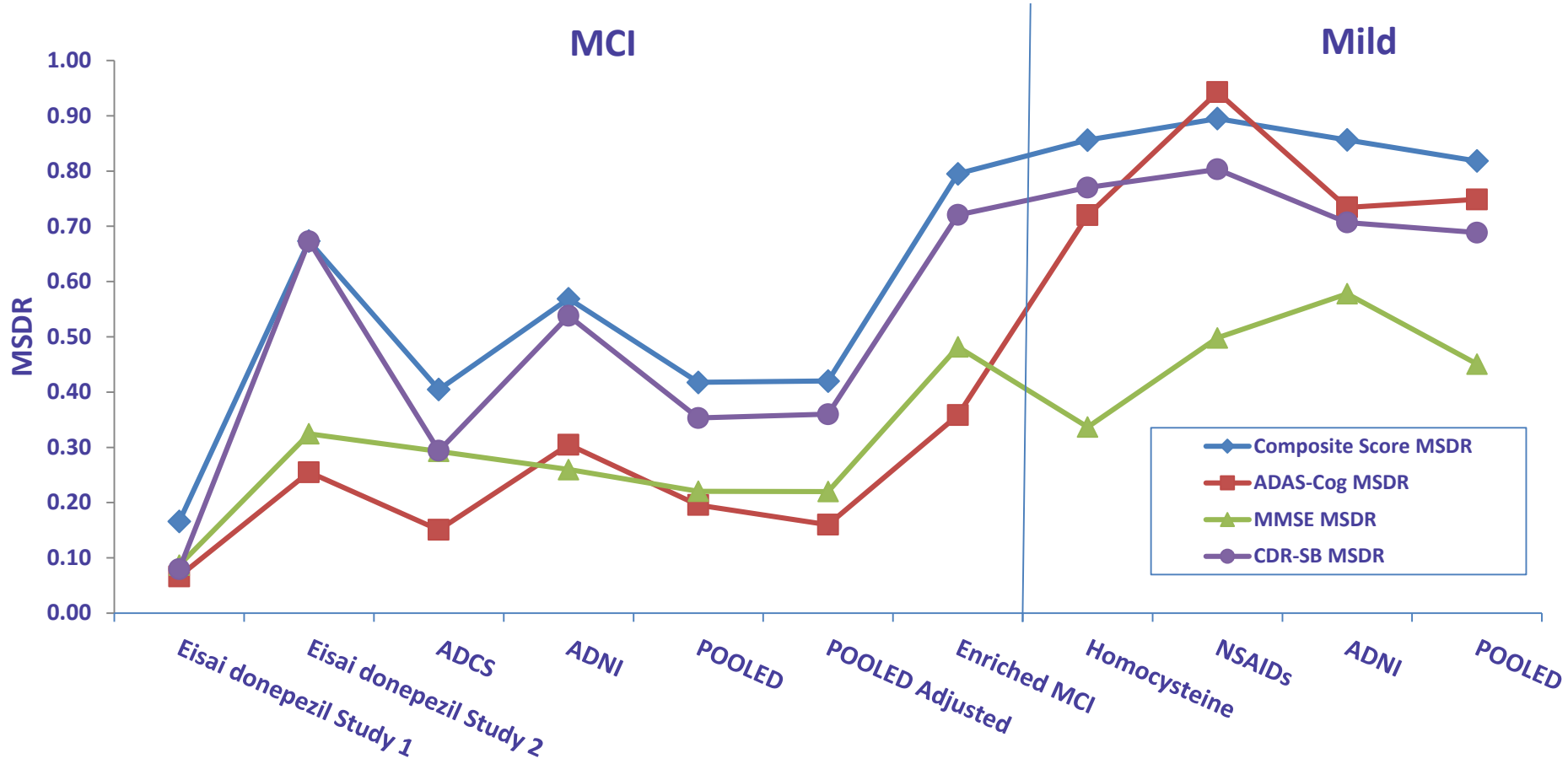
# Items and Their Relative Contributions

| | | Maximum Possible | % of Composite | Observed Maximum | % of Composite Observed |
|---|---|---|---|---|---|
| ADAS | Delayed Word Recall | 10 | 4% | 10 | 6% |
| | Orientation | 8 | 7% | 7 | 9% |
| | Word Recognition | 12 | 2% | 12 | 3% |
| | Word Finding Difficulty | 5 | 4% | 4 | 4% |
| MMSE | Orientation to Time | 5 | 11% | 5 | 15% |
| | Constructional Praxis | 1 | 2% | 1 | 3% |
| CDR | Personal Care | 3 | 8% | 1 | 4% |
| | Community Affairs | 3 | 17% | 2 | 15% |
| | Home and Hobbies | 3 | 14% | 2 | 13% |
| | Judgment and Problem Solving | 3 | 11% | 2 | 10% |
| | Memory | 3 | 9% | 2 | 8% |
| | Orientation | 3 | 12% | 2 | 11% |

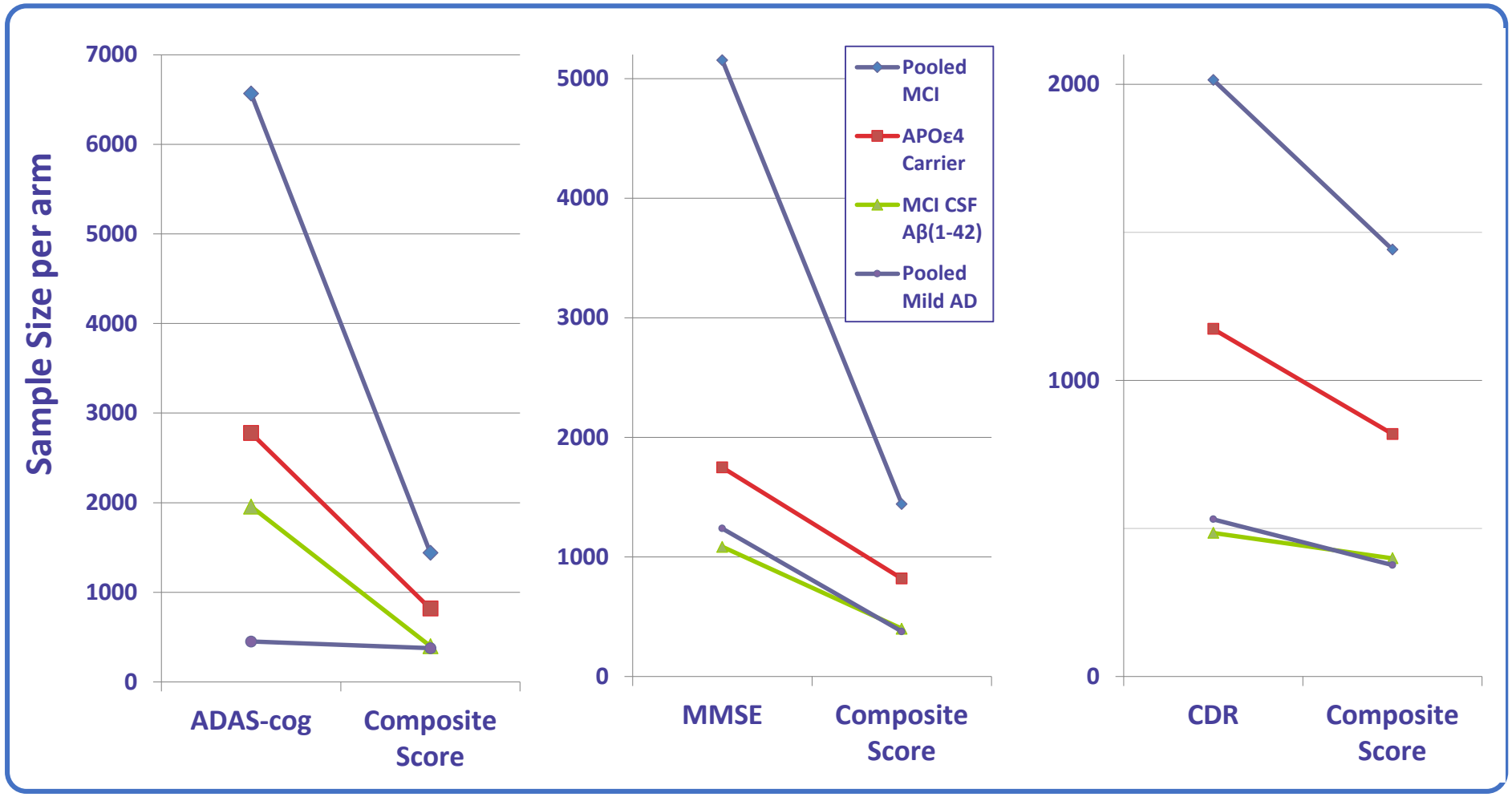
- **ADAS-cog items contribute ~22% *(vs. ~17% if maximum values assigned)***
- **MMSE items contribute ~18% *(vs. ~13% if maximum values assigned)***
- **CDR-sb items contribute ~61% *(vs. ~71% if maximum values assigned)***

# ADCOMS Shows High Sensitivity and Reliability in MCI and Mild Dementia




- ***Across multiple studies and populations ACOMS is consistently better than established scales***
- ***If combination tool is based only on enriched (Aβ42 positive) MCI patients, it has similar sensitivity to ADCOMS in enriched MCI population, but lacks reliability (data not shown)***

# ADCOMS Improves Responsiveness/Sample Size Required Compared to Original Scales



# Responsiveness to Treatment Effect: Difference of Donepezil Versus Placebo in Change from Baseline

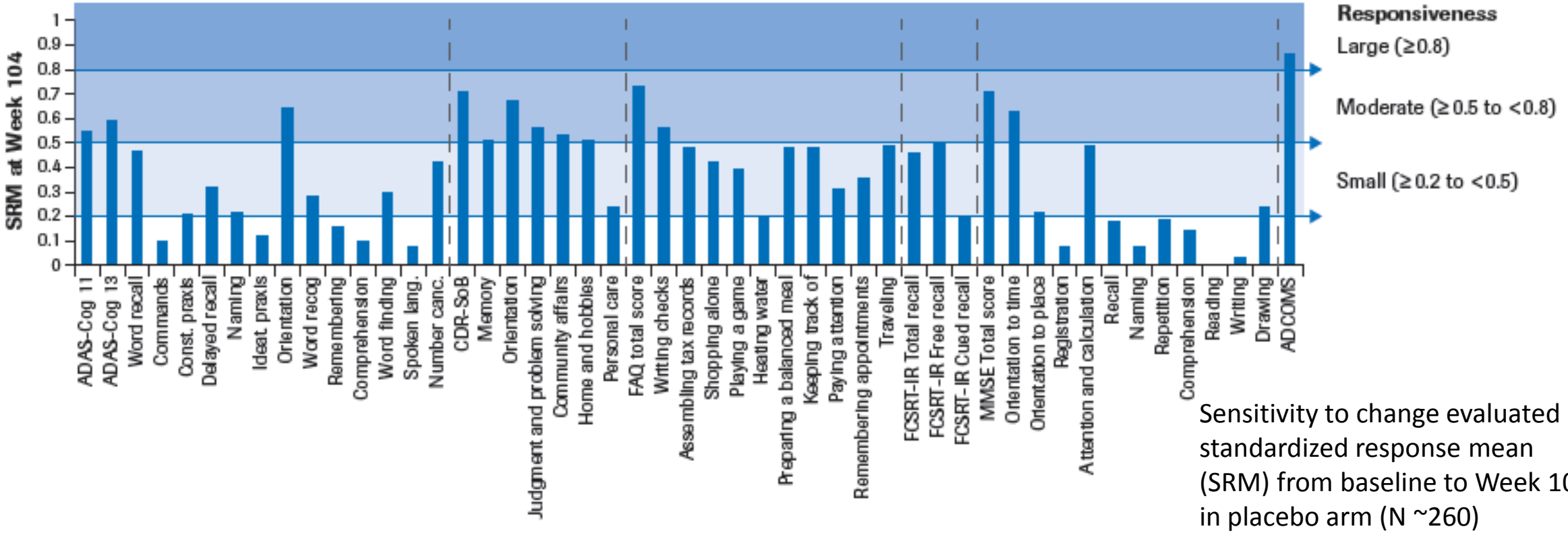
| Study | Population | Study duration | Treatment† | ADAS-Cog | CDR-SB | MMSE | Composite |
|---|---|---|---|---|---|---|---|
| Eisai donepezil Study 1 | MCI | 12 mo | 10 mg | - | - | - | - |
| Eisai donepezil Study 3 | Mild AD | 6 mo | 5 mg | + | - | + | + |
| | | | 10 mg | + | - | - | + |
| ADCS | MCI | 12 mo | 10 mg | - | - | + | + |
| | | | 2000 IU Vitamin E | - | - | - | - |

+ indicates statistical significance at alpha=0.05; - indicated statistical significance was not reached
† Treatment was donepezil unless otherwise indicated

- Responsiveness to treatment effect is driven by combination of all three scales
- CDR-sb alone is not responsive to treatment effect

# Data from Phase 3 Scarlet RoAD Study with Gantenerumab: First Independent Study to Confirm Sensitivity of ADCOMS

**Figure 1: Responsiveness to decline**

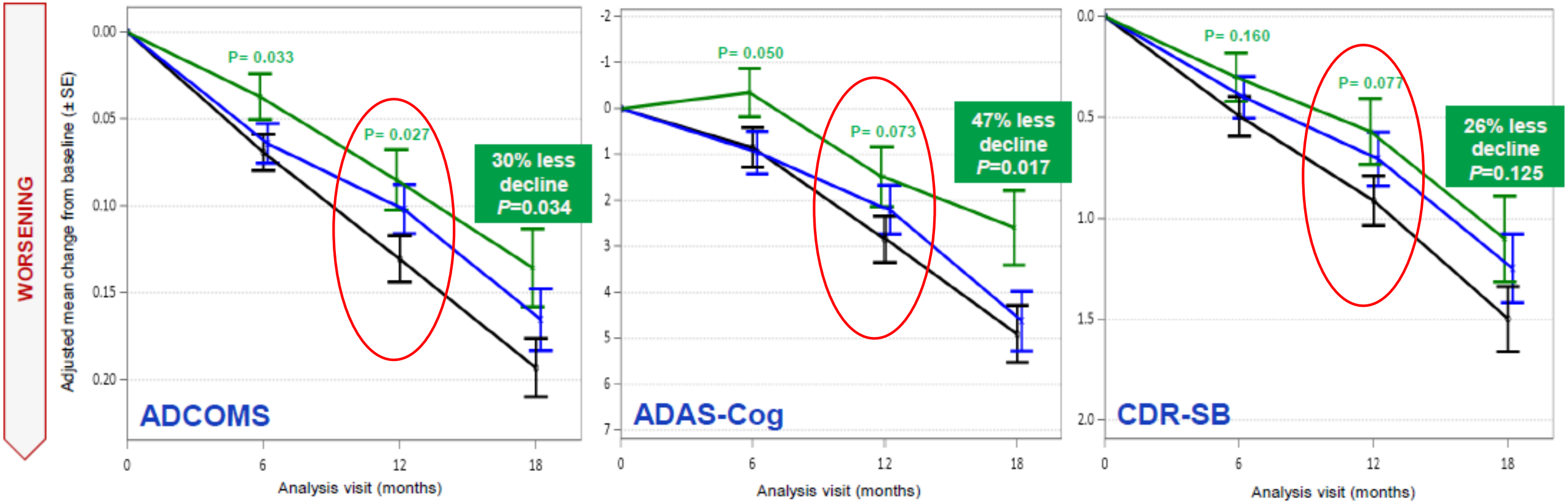



Sensitivity to change evaluated as standardized response mean (SRM) from baseline to Week 104 in placebo arm (N ~260)

ADCOMS = ADAS-Cog Delayed Word Recall * 0.00847483 + ADAS-Cog Orientation * 0.017088 + ADAS-Cog Word Recognition *0.003732761 + ADAS-Cog Word Finding Difficulty * 0.016211 + (5 - MMSE Orientation to Time) * 0.041567 + (1 - MMSE Drawing) * 0.038238 + CDR Personal Care * 0.054321 + CDR Community Affairs * 0.109100 + CDR Home and Hobbies * 0.089039 + CDR Judgment/Problem Solving * 0.069493 + CDR Memory * 0.058724 + CDR Orientation * 0.078152

From “Comparative traditional psychometrics of cognitive and functional endpoints in a prodromal Alzheimer’s disease population” by Chris Edgar et al., 2015 presented by Roche Clinical Trials on Alzheimer's Disease, (Volume: Volume 2, Number 4)

# EISAI Presentation of BAN2401 Data: ADCOMS Shows Higher Sensitivity to Decline Compared to ADAS-Cog and CDR-SB at 12 months




| N with data | 0 mo. | 6 mo. | 12 mo. | 18 mo. |
|---|---|---|---|---|
| Placebo | 238 | 216 | 187 | 160 |
| 10 mg/kg monthly | 246 | 208 | 165 | 146 |
| 10 mg/kg bi-weekly | 152 | 130 | 93 | 79 |

Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models.

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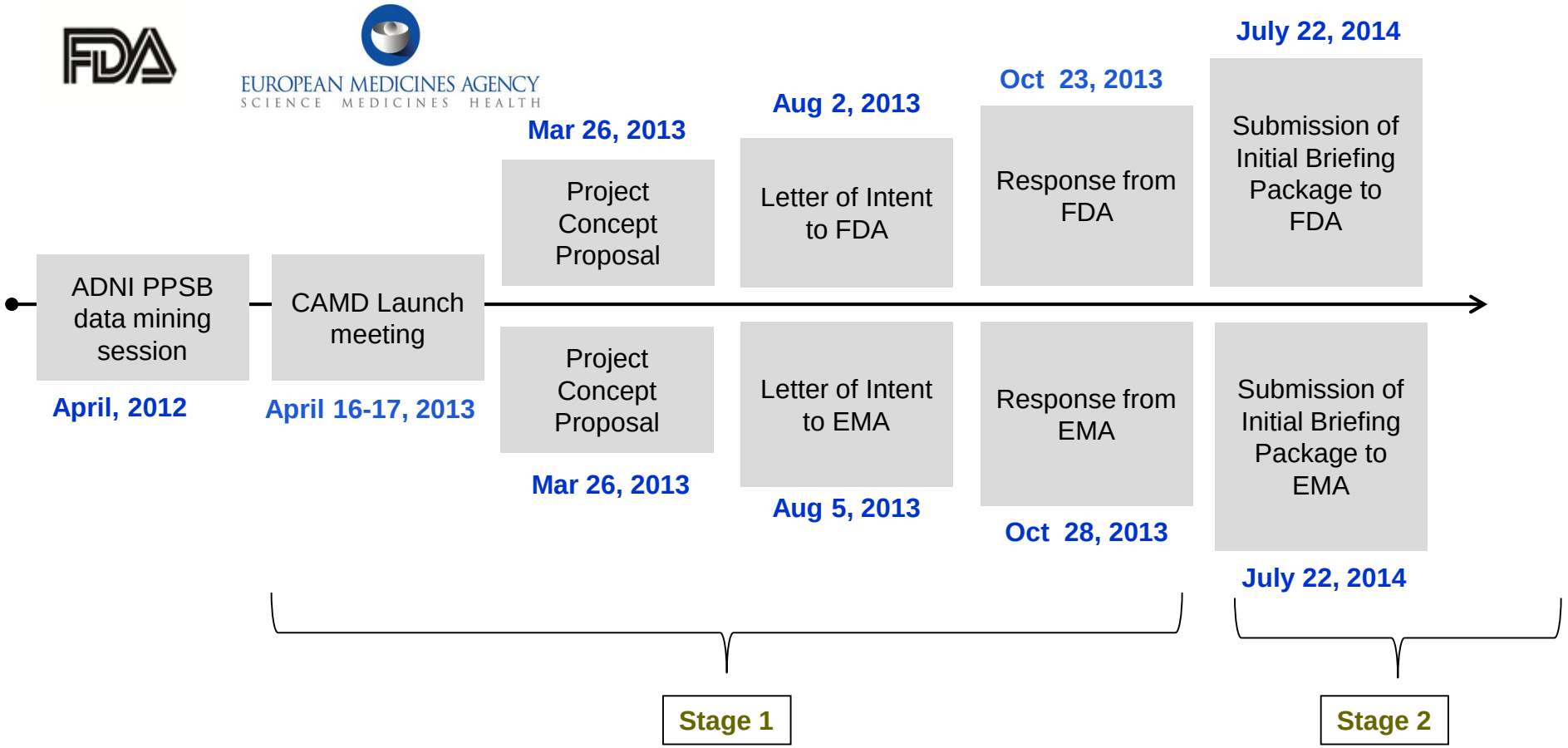
Presented at the 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

# Regulatory Qualification: CAMD pCOA Project

*FDA and EMA collaborated on Clinical Outcome Assessment project to qualify ADCOMS with aim to harmonize all stages*




- Project stopped during Stage 2 after meetings with regulators
- Concerns (particularly by FDA) about evidence-based approach to increase sensitivity of clinical outcome

# Conclusions

- ADCOMS is novel tool made up of a combination of key sensitive items from existing scales
- Uses evidence-based approach (not traditional psychometric development)
- Optimized for decline over 12 months  in prodromal AD as a weighted linear combination of these items
- Shows improved sensitivity to decline compared to current scales
- Enables dramatic reductions in required sample sizes/arm for 12+ month treatment trials in MCI
- Captures response to treatment effects
- Has been validated in prospective studies
- Regulatory support for ADCOMS is unclear