New approaches to cognitive endpoints in confirmatory trials of Early Alzheimer's Disease (EAD)

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Disclosures

- Judith Jaeger is owner and Principal Scientist at CognitionMetrics, LLC. Over the past year, CognitionMetrics has had contractual relationships for scientific and advisory services with: Apex, Biogen, CenExel, Cumulus, Cyclerion, INmuneBio, Jazz, Lundbeck, JnJ, Osmol, Shackelford, Umecrine, VigilNeuro.

Alzheimer's disease: Definition

- **A brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. People with Alzheimer's also experience changes in behavior and personality**

https://www.alzheimers.gov/alzheimers-dementias/alzheimers-disease

CONCEPT OF INTEREST = Cognitive, functional and behavioral CHANGE

Cognitive Change is the PARAMOUNT Concern of aMCI patients and their partners

- 100% of (N=25) informants and 100% of (N=25) patients with aMCI indicated Memory was a concern
- Other complaints, not universally reported, reflect differences among participants in ways memory problems are manifested, i.e. forget names, effect of memory problems on verbal expression.
- Other complaints, also not universal, included changes in social Interaction, impact on social functioning, irritability, employment status, insight into problems, impact on driving, daily activities, likely reflect a combination of cognitive and behavioral changes and their impact on functioning.

(Ropacki, 2017)

Why new cognitive endpoints for EAD are needed

Measure what matters!

- ADAS-Cog, the currently accepted primary cognitive endpoint was designed to capture cognitive *deficits* in “mild to moderate” AD patients.

- These are not the same cognitive *changes* that occur during Early AD.

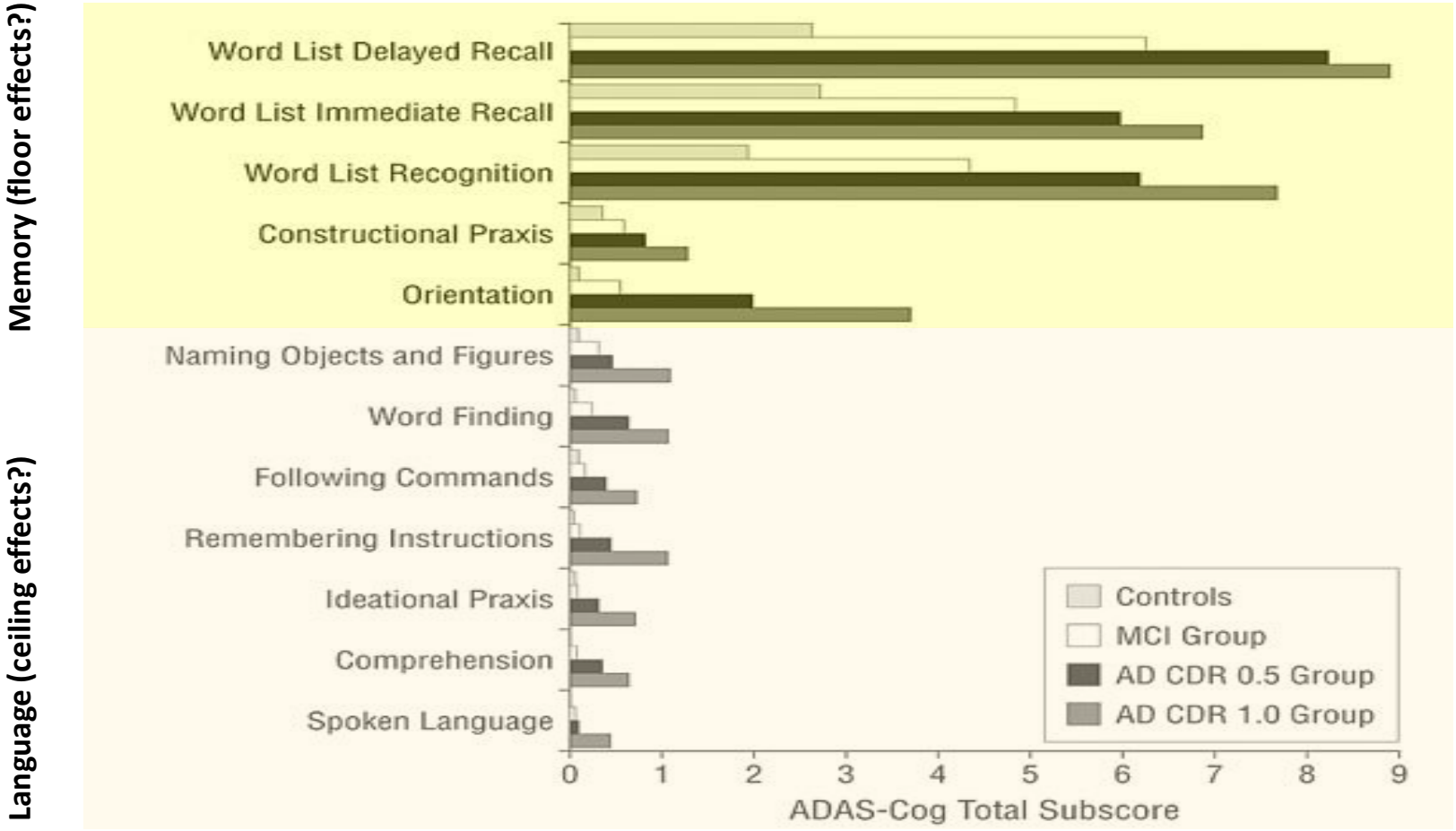

Figure adapted from Grundman MPH et al. (2004).

ADAS-Cog is not suitable for EAD trials

"If the ADAS-Cog cannot detect important changes, our understanding of pre-dementia disease progression may be compromised and trials may incorrectly conclude that a novel treatment approach is not beneficial."

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Review

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review

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New cognitive endpoints for EAD are needed

- **Cognitive test scores that do not change in the population of interest over the time period of interest are not relevant and fall outside the concept of interest.**

We need endpoints that are psychometrically "sound" reflections of the concept of interest

- Should be empirically derived and validated
- Have no floor or ceiling effects
- Minimized within subject variance
- Valid for sufficiently short retest intervals

Why is this important?

The field needs an ACCURATE measure of MEANINGFUL cognitive change… → Reduces overall study burden (fewer patients/ shorter trials) → Provides clearer and more rapid decisions (faster to market).

Background

EMACC was first developed in 2017 with the support of Lundbeck Pharma with the goal of finding a replacement for the ADAS-Cog that would measure cognitive changes that occur in Early AD[1].

EMACC was developed to provide an accurate measure of cognitive change in EAD patients in global trials using a collection of familiar, widely used and validated neuropsychological tests.

[1] Jaeger, J., Hagen, C.E., Loft, H., et al. The Early AD/ MCI Alzheimer's Cognitive Composite (EMACC): Development and preliminary validation across four longitudinal cohorts of a cognitive endpoint for clinical trials in the MCI and Early AD stage of disease. Presented at: CTAD November 2017

REVIEW FROM CTAD 2017:
EMACC: Development & preliminary validation across four longitudinal cohorts of a cognitive endpoint for clinical trials in MCI and Early AD stage disease

- **Jaeger, J., Hagen, C, Loft, H., Lim, YY, Aschenbrenner, A., Segerdahl, M, Tong, G., Mielke, M., Hassenstab, J., Stricker, N.**

Samples studied:

	ADNI		AIBL		WUSTL		MCSA	
	CN AB-	MCI AB+	CN AB-	MCI AB+	CN AB-	MCI AB+	CN AB-	MCI AB+
N (baseline)	186	237	278	121	155	57	548	101
N Year 2	163	192	278	121	155	44	432	62
N Year 3	84	156	233	69	135	33	337	47
N Year 4	117	111	178	36	114	24	214	28

1. **ADNI: Alzheimer's Disease Neuroimaging Initiative**
2. **AIBL: Australian Imaging, Biomarkers and Lifestyle Study**
3. **WUSTL: Washington University, St. Louis Knight ADRC**
4. **MCSA: Mayo Clinic Study of Aging**

EMACC: Methods*

1. **Included for consideration only neuropsychological (NP) tests readily subject to linguistic & cultural adaptation which can be reliably administered by a non-neuropsychologist (to assure suitability for global trials). (Selected by an expert advisory board).**
2. **In each cohort, standardized slopes were computed within the Aβ+ MCI group on all possible combinations of composites containing between 4 and 8 NP test variables.**
3. **Results were rank ordered according to magnitude of slope @years 2, 3 and 4 post-baseline**
4. **The EMACC was constructed based on the pattern of individual tests falling in the top ranked composites in each cohort at all time points. The final EMACC was the "winner" at year 2 (i.e. greatest slope across all four cohorts).**
5. **A series of linear mixed models (LMM) were then conducted between the Aβ- CN and Aβ+ EAD/MCI, on EMACC and other benchmarks (e.g., CDR Sum of Boxes, MMSE).**
6. **Cohen's d effect sizes were computed and used to examine change from baseline to years 2,3 and 4 and to compare the magnitude of cognitive decline between various outcome measures.**

*Jaeger et al, 2017

EMACC RESULTS*
FINAL MEASURES IN EACH COHORT

		ADNI		AIBL		WUSTL		MCSA	
Domain	Paradigm	Test	Measure	Test	Measure	Test	Measure	Test	Measure
Memory	*Word list learning*	RAVLT	Trials 1-5	CVLT	Trials 1-5	FCSRT	Free Recall	RAVLT	Trials 1-5
	Digit Span			WAIS-R DS	Forw+Back	WAIS-R DS	Forward		
Executive + Psychomotor	*Fluency*	Category fluency	Animals	Category fluency Letter Fluency	Animals FAS	Category fluency Letter Fluency	Animals+ Vegetables FAS	Category fluency	Animals+fruits+ vegetables
	Trailmaking *Conflict Inhibition*	Trailmaking Test	Trails A (secs) Trails B (secs)	Stroop	Color naming speed (secs)	Trailmaking Test	Trails A (secs) Trails B (secs)	Trailmaking Test	Trails A (secs) Trails B (secs)
	Coding	ADAS Number Canc	Total score	DSST	Total score	DSST	Total score	DSST	Total score

*Jaeger et al 2017

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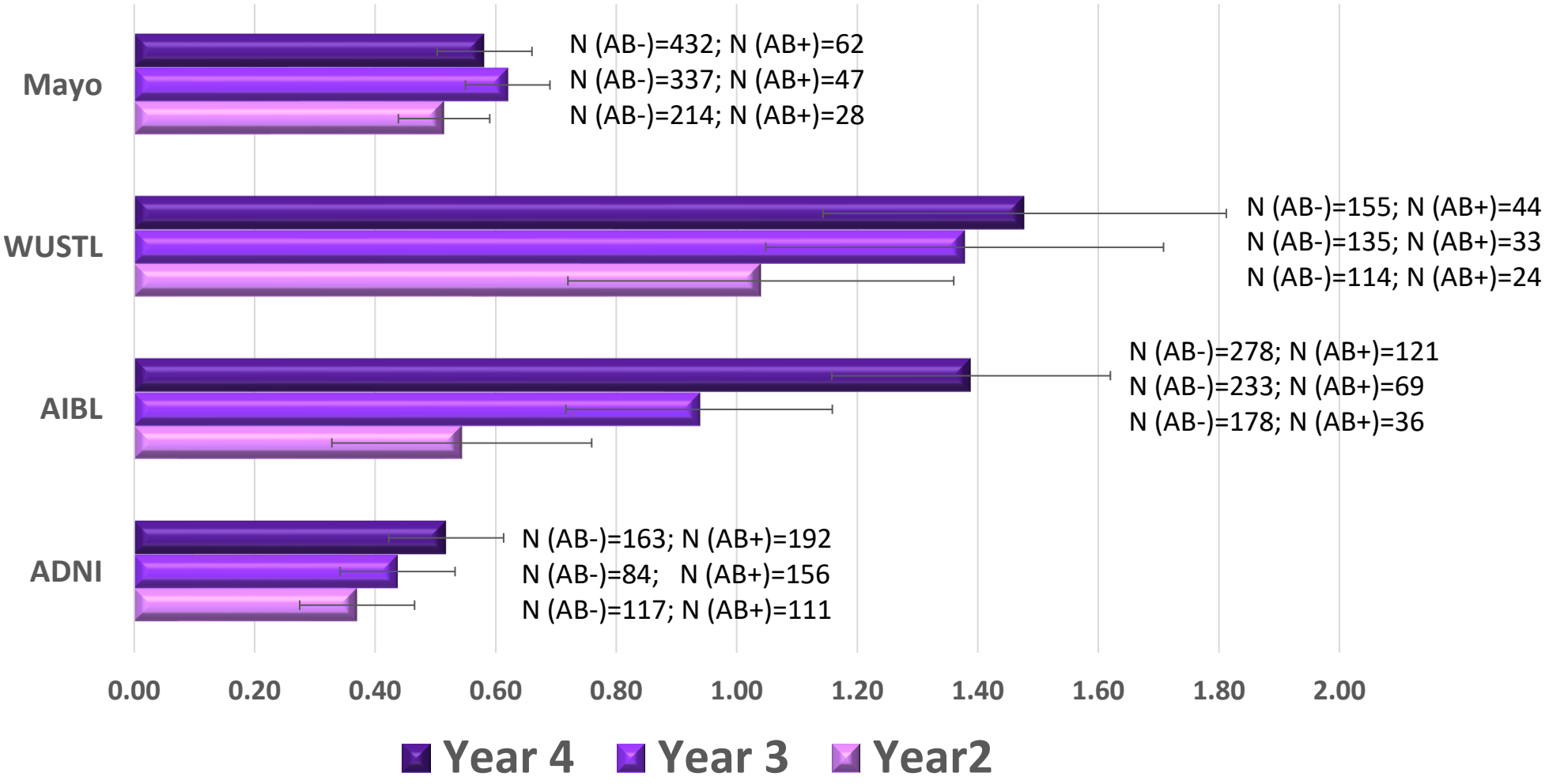
*Jaeger et al, 2017

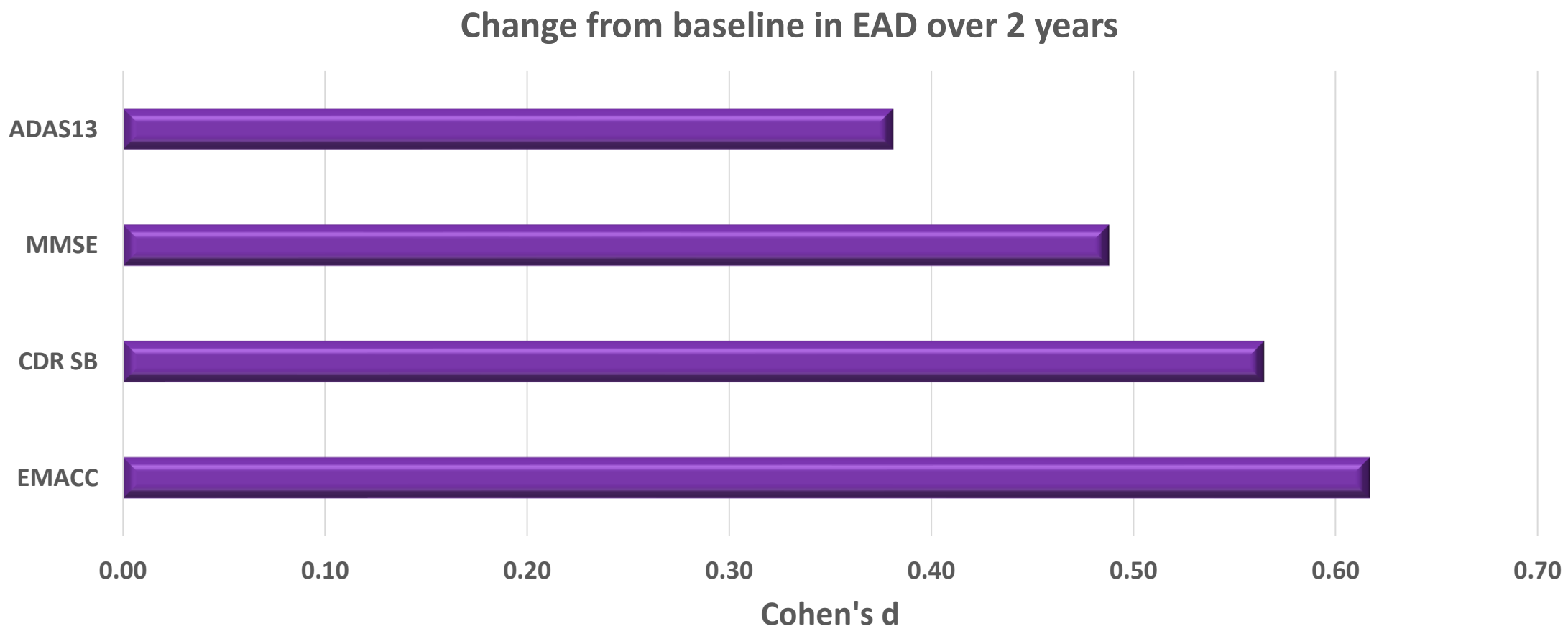
EMACC RESULTS *
COHEN'S d EFFECT SIZES BY TIME POST BASELINE



Substitutions:
ADNI: Symbol Coding for Symbol Coding
AIBL: Stroop for Trailmaking A&B

*Jaeger et al, 2017

EMACC RESULTS 3 of 3*
MEAN EFFECT SIZE CHANGE OVER 2 YEARS IN 4 LONGITUDINAL COHORTS



Notes: ADAS13 only available in ADNI Cohort; AIBL excluded from CDR SB data due to substantial deviation in standard administration procedures.

Conclusions about EMACC

All tests in the EMACC are:

- Validated, widely known and in use for decades by neuropsychologists.
- Normally distributed in EAD (has no floor or ceiling effects)
- Optimized to detect change in cognitive symptoms relevant to EAD
- Includes memory AND executive functioning measures

What tests comprise the EMACC?

- **Word list learning**, immediate only (e.g. RAVLT, ISLT, ADAS-Cog word list)
- **Digit Span forward and backward**
- **Category fluency (DKEFS)**
- **Letter Fluency (DKEFS)**
- **Trailmaking A and B**
- **Digit Symbol Coding (WAIS)**

EMACC does not increase patient burden:

- **EMACC**: 30-45 minutes
- **ADAS-Cog**: 35-45 minutes
- **CDR**: 30-50 minutes

Proof of Concept for EMACC in Biogen TANGO study

Shulman et al **(LBR5). Top-line results from TANGO, a Phase 2 study of gosuranemab in participants with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease. On demand.*

TANGO Trial

NCT03352557

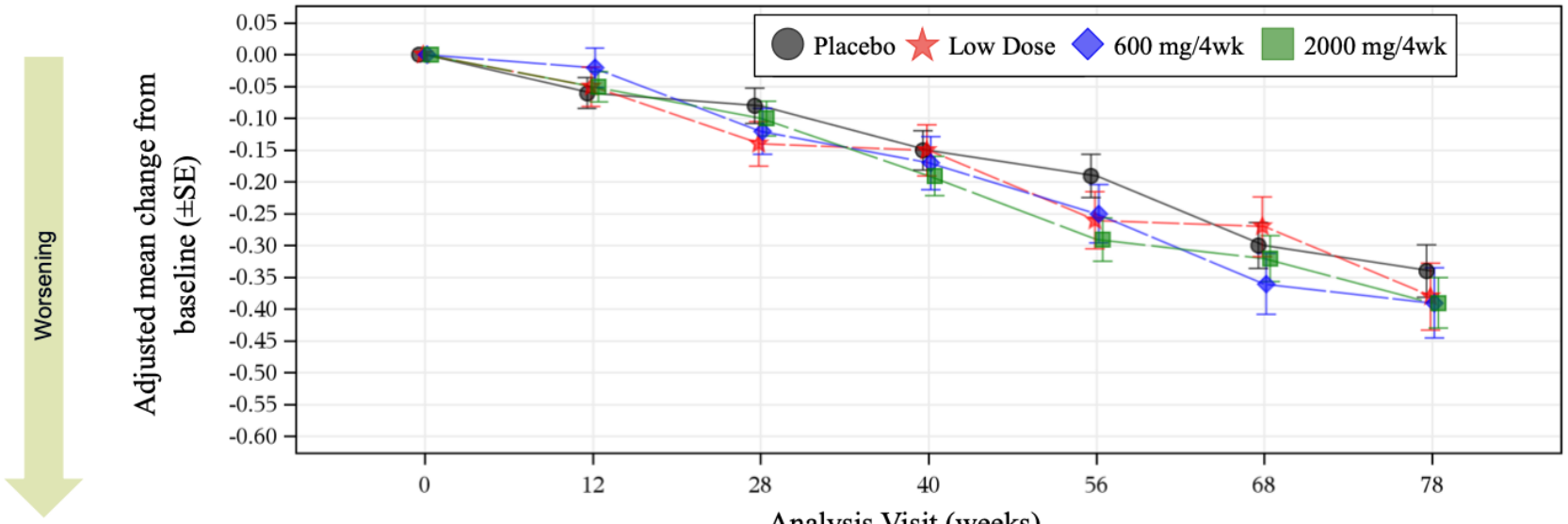
101 Sites: US, Germany, Japan, Poland, Spain, Sweden, Italy, France, Australia

EMACC was administered every 3 months; ADAS-Cog & CDR every 6 months.

RESULTS: EMACC illustrated a smooth monotonic cognitive decline in the placebo group (indeed in all groups) with less fluctuation over time than shown by CDR or ADAS-Cog.

TANGO: A Phase 2 study of gosuranumab in EAD

Longitudinal changes from baseline on EMACC to Week 78



Number of Subjects

Placebo	214	194	182	164	146	145	152
Low Dose	116	101	105	96	80	81	84
600mg/4wk	106	96	95	81	73	80	76
2000mg/4wk	214	193	189	172	152	149	152

No P-value < 0.05 versus placebo at Week 78

Analysis based on MMRM model, with fixed effects of treatment group, time (categorical), treatment group by time interaction, baseline EMACC, baseline EMACC by time interaction, MMSE baseline, AD symptomatic medication use, region and disease stage (MCI vs mild AD dementia).

EMACC is a composite score of ISLT, DKEFS (Category Fluency total correct score & Letter Fluency total correct score), DSST, and Trails.

AD, Alzheimer's disease; DKEFS, Delis-Kaplan Executive Function System; DDST, Digit Symbol Substitution Test; EMACC, Early Alzheimer's Disease/Mild Cognitive Impairment Cognitive Composite; ISLT, International Shopping List Test; MCI, mild cognitive impairment; MMRM; mixed model for repeated measure; MMSE, Mini-Mental State Exam; SE, standard error; wk, weeks.

Greater effect size change with EMACC in ADNI cohort (in AD with Neuroinflammation ("ADi"))

Biomarker	ADAS-Cog13 change over 12 months			Change in CDR-SB over 12 months			Change in EMACC composite over 12 months[2]		
	N	Mean (SD)	ES	N	Mean (SD)	ES	N	Mean (SD)	ES
None	428	1.79 (5.29)	0.33	437	0.22(0.42)	0.52	437	-0.13(0.37)	0.37
CRP ≥ 1.5 mg/L AND APOE4+	64	2.84(6.12)	0.46	66	0.20(0.40)	0.50	66	-0.25(0.33)	0.76

[1] CDR score=0.5 or 1.

[2]Note: EMACC composite score excludes Symbol Digit Coding which is not available in these ADNI subjects.

Statistical power in ADi:

(1:1 randomization, 80% power, 2-sided test, α=0.05)

(Placebo assumptions are taken from actual effect size change over 12 months in ADNI)

Endpoint	Placebo Assumptions Mean	INB03 Assumptions Mean	Difference	Common SD	N/arm	Total N	15% drop out rate
EMACC	-0.25	0	0.25	0.33	28	**56**	66
CDR-SB	0.20	0	0.2	0.4	63	**126**	150
ADAS-13	3	0	3	6.1	65	**130**	154

These estimates are based upon two measurements (baseline and 12 month followup.)

Another way to increase power is to measure more often.

Summary and Conclusions - 1

For clinical trials in Early AD, ADAS-Cog 13 is unsuitable.
It does not meet FDA guidance standards in terms of the concept of interest in this population, nor does it fulfill psychometric requirement of lack of ceiling effect.

In contrast, the EMACC meets these requirements. Further:

- **EMACC has greater dynamic range to detect change in the appropriate cognitive symptoms**
- **EMACC showed better signal to noise ratios (lower variance) in Tango**
- **EMACC can be administered more frequently, permitting more powerful designs that reduce the within subject noise from day to day variance.**

Summary and Conclusions - 2

EMACC was developed in a strictly empirical manner

- **It is a collection of established and well validated neuropsychological tests selected for optimized power to detect disease progression in four independent cohorts of biomarker confirmed MCI patients.**

EMACC has been used in a completed global trial (TANGO) where it demonstrated superior stability and power to detect progression of cognitive symptoms relevant in EAD.

EMACC will be the primary endpoint in INmune Bio's phase 2 trial of XPro1595 in ADi

Summary and Conclusions - 3

- **At least two cognitive testing CRO's have developed computer assisted versions of the EMACC for use in global (multi-lingual) trials.**
- **We fully expect that ongoing psychometric work from these trials will provide the additional validation required by regulatory bodies that will allow EMACC to be used as a primary cognitive endpoint for pivotal trials.**

Limitations and Challenges

- **In the development cohort, the EMACC consisted of a range of different actual tests using similar or identical paradigms. Will regulators accept as equivalent indices of change, if different studies use for their EMACC different tests with comparable paradigms (i.e. word list learning)?**
- **The EMACC consists of one actual and several potential proprietary instruments. Can non-proprietary instruments with similar paradigms be used as a substitute?**