Evaluating the Evidence of Aducanumab Treatment Benefit Using Standardized Test Statistics and Global Statistical Tests

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Disclosures

- SD is an employee of Pentara Corporation and SH is an employee and owner of Pentara Corporation, a company that consults for Biogen
- SB, SBH, CC-V, PH, JM, and YT are employees of Biogen and may be stockholders
- LY was an employee of Biogen at the time of this work and has since left the company
- PA is a consultant to Biogen
- Writing and editorial support for the preparation of this presentation was provided by MediTech Media (Atlanta, GA, USA); funding was provided by Biogen
- Aducanumab is approved for use in the following markets: the United States, the United Arab Emirates, and Qatar. In the rest of the world, it is an investigational drug. Its efficacy and safety have not been established in Spain

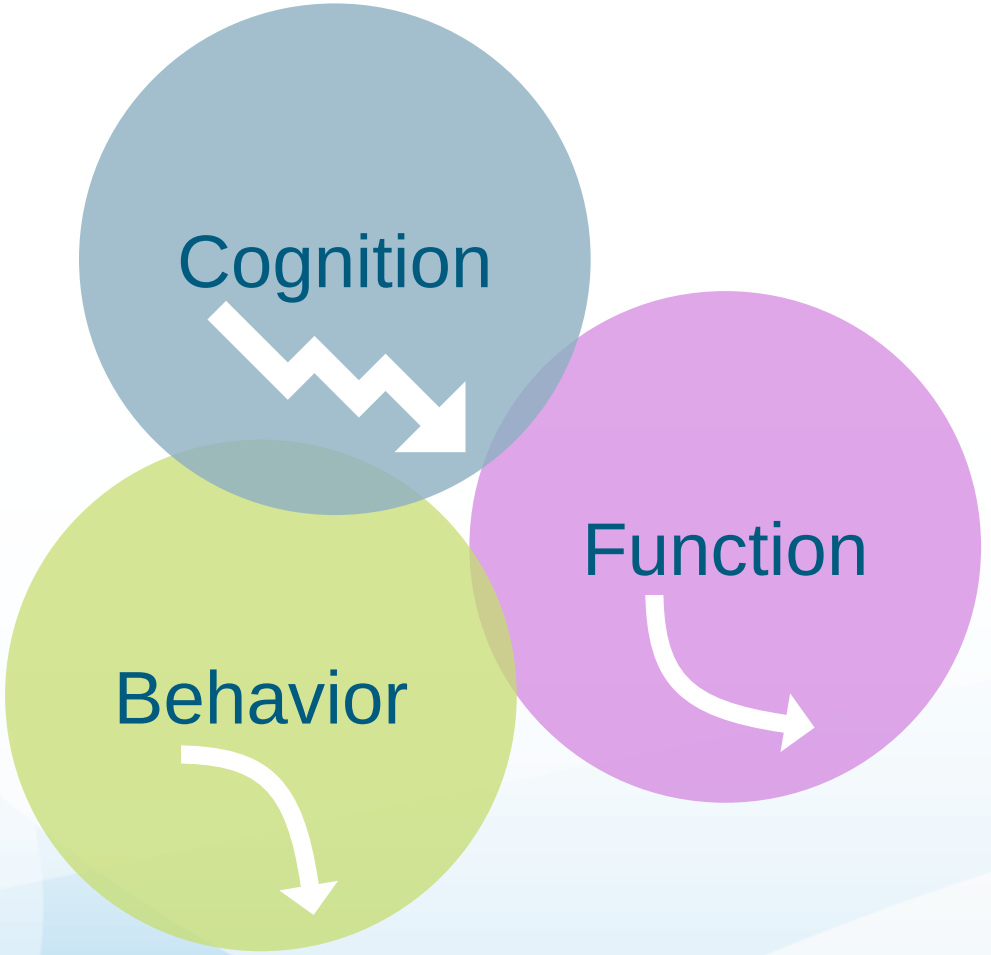
Statistical evidence in EMERGE and ENGAGE:

Are the results due to a chance or real treatment effects?

- Statistical evidence, clinical meaningfulness, and safety should be considered separately
- Traditional clinical endpoints have inherent challenges and are misaligned with disease progression when used individually
- The degree of difficulty in Alzheimer’s disease clinical trials leaves little room for error

Alzheimer's disease is a progressive and heterogeneous neurodegenerative disorder[1,2]

- Disease course measurement is complex due to variability in the rate of disease progression[3,4]
- Disease severity and symptom assessment are also complicated by heterogeneous disease features[5]
  - Clinical phenotypes of Alzheimer's disease involve different domains[1,5,6]
- Several validated assessments are widely adopted in clinical practice to detect/monitor Alzheimer's disease across domains[6]



1. Alzheimer's Association. *Alzheimers Dement*. 2021;17(3):327-406; 2. Devi G, Scheltens P. *Alzheimers Res Ther*. 2018;10(1):122; 3. Thalhauser CJ, Komarova NL. *J R Soc Interface*. 2012;9(66):119-126; 4. Samtani MN, et al. *Br J Clin Pharmacol*. 2013;75(1):146-161; 5. Friedland RP, et al. *Ann Intern Med*. 1988;109(4):298-311; 6. Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8(3):371-386.

Phase 3 clinical trials of aducanumab

- Aducanumab is a monoclonal antibody that selectively targets aggregated soluble Aβ oligomers and insoluble Aβ fibrils[1,2]

- **EMERGE (NCT02484547)** and **ENGAGE (NCT02477800)** were identically designed, randomized, double-blind, placebo-controlled Phase 3 studies of aducanumab in patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia[3,4]

Aβ, amyloid beta; MCI, mild cognitive impairment.

1. Sevigny J, et al. *Nature*. 2016;537(7618):50-56; 2. Arndt J, et al. *Sci Rep*. 2018;8(1):64124; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02484547 Accessed February 21, 2021; 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477800 Accessed February 21, 2021.

Phase 3 clinical trials of aducanumab

March 2019
Studies halted following futility analysis of EMERGE and ENGAGE[6]

2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021

Development of aducanumab using Reverse Translational Medicine Technology (2007)[1]

FDA filing and acceptance of BLA for aducanumab[6]

Aducanumab was approved by FDA for the treatment of Alzheimer's disease[7,a]

Identical study designs

Phase 3: ENGAGE[2,3]
N=1653; placebo-controlled (Months 1-18), parallel-group study in early AD, low/high dose (global)

LTE

Phase 3: EMERGE[2,4]
N=1643; placebo-controlled (Months 1-18), parallel-group study in early AD, low/high dose (global)

LTE

Primary endpoint[5] CDR-SB at Week 78
Secondary endpoints[5] MMSE, ADAS-Cog 13, and ADCS-ADL-MCI
Other endpoints include cerebral Aβ plaques as measured by PET at Weeks 26 and 78[5]

Phase 3b: EMBARK[8,9]
Screened 1856 participants (1694 enrolled)[b]; open-label re-dosing study

Aβ, amyloid beta; AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); BLA, Biologics License Agreement; CDR-SB, Clinical Dementia Rating–Sum of Boxes; FDA, US Food and Drug Administration; LTE, long-term extension; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10 items); PET, positron emission tomography; PK, pharmacokinetics.

[a] According to the US prescribing information, aducanumab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials[9]; [b] As of July 15, 2021.[11]

1. Neurimmune. Reverse Translational Medicine™ Technology Platform, 2016. https://www.neurimmune.com/technology/rtm-technology-platform Accessed February 21, 2021; 2. Castrillo-Viguera C, et al. CTAD 2020; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477800 Accessed February 21, 2021; 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02484547 Accessed February 21, 2021; 5. Budd Haeberlein S, et al. ADPD 2021; 6. Combined FDA and applicant PCNS Drugs Advisory Committee briefing document. US Food and Drug Administration website. Published November 6, 2020. Accessed February 21, 2021; 7. Aduhelm (aducanumab). Prescribing information. Biogen, Inc.; 2021; 8. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04241068 Accessed February 21, 2021; 9. Cohen S, et al. CTAD 2021.

EMERGE and ENGAGE efficacy results

Low-dose aducanumab group from EMERGE and ENGAGE were consistent

High-dose aducanumab group from EMERGE and ENGAGE were partially inconsistent

Diff vs placebo (%)[a]	Low-dose aducanumab		High-dose aducanumab	
	ENGAGE N=547	EMERGE N=543	ENGAGE N=555	EMERGE N=547
CDR-SB	-0.18 (-12%)	-0.26 (-15%)	0.03 (2%)	**-0.39 (-22%)**
MMSE	0.2 (-6%)	-0.1 (3%)	-0.1 (3%)	**0.6 (-18%)**
ADAS-Cog 13	-0.58 (-11%)	-0.70 (-14%)	-0.59 (-11%)	**-1.40 (-27%)**
ADCS-ADL-MCI	0.7 (-18%)	0.7 (-16%)	0.7 (-18%)	**1.7 (-40%)**
Amyloid-PET[b] SUVR (centiloid unit)	**-0.167 (-38.5)**	**-0.179 (-41.3)**	**-0.232 (-53.5)**	**-0.278 (-64.2)**

***p*<0.05 favoring aducanumab**

Numeric advantage favoring aducanumab

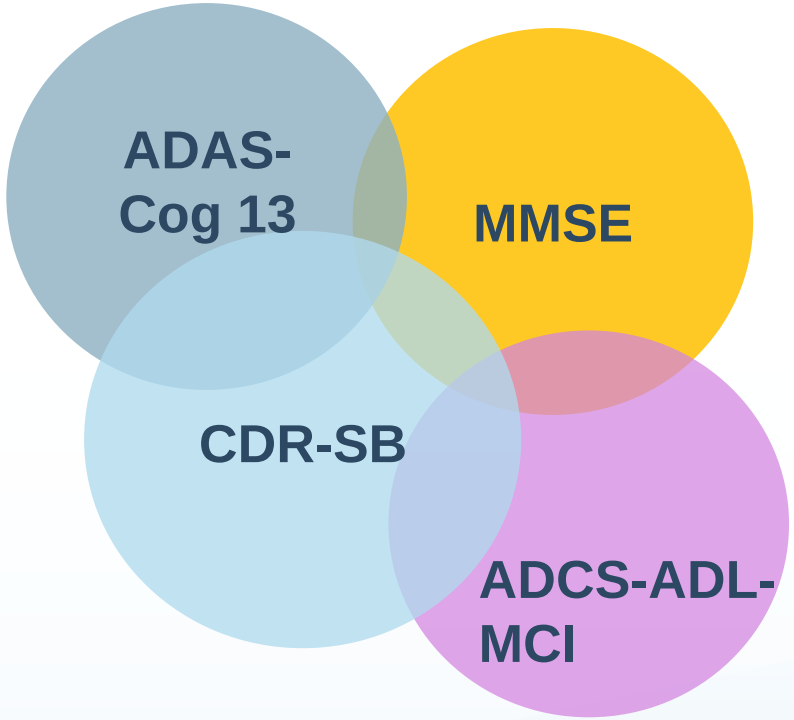
No numeric advantage favoring aducanumab

N = numbers of randomized and dosed participants.
[a] Difference vs. placebo at Week 78; [b] Number of participants in ENGAGE PET substudy = 585 and EMERGE substudy = 488.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SUVR, standardized uptake value ratio.
Budd Haeberlein S, et al. ADPD 2021.

Clinical endpoints measure distinct, important symptoms of cognition, function, and global performance

Clinical efficacy rating scales were used in EMERGE and ENGAGE

- Validated and widely used in early Alzheimer's disease
- Includes key perspectives:
  - Expert clinical judgment based on patient examination and caregiver input
  - Patient and caregiver reports
  - Cognitive performance tests
- Collectively they measure many distinct elements and cover the various symptoms experienced by patients with Alzheimer's disease **with each contributing unique information**



ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10 items).

Statistical methodologies and objectives[1,2]

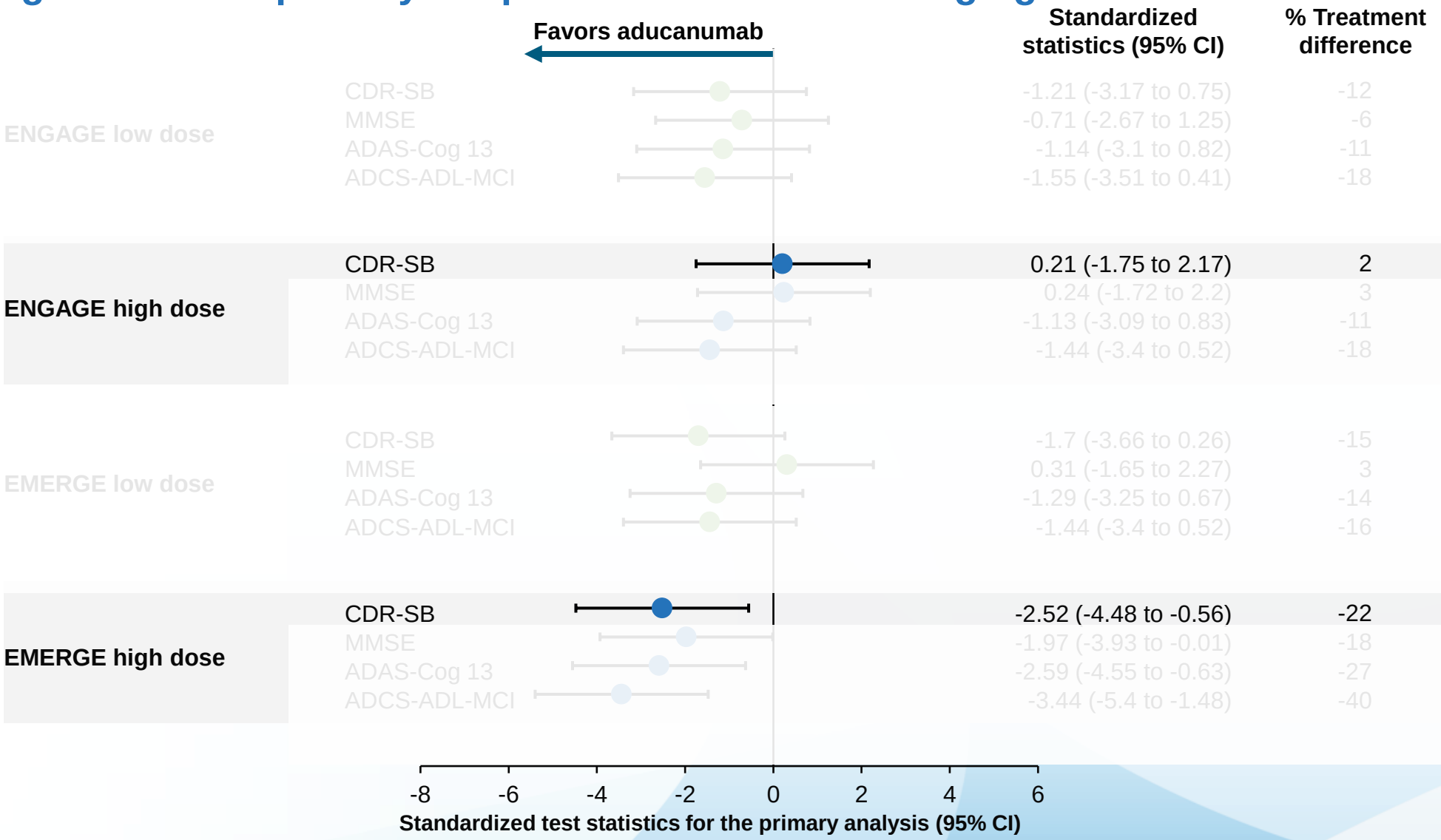
Standardized test statistics allow for a comparison of results across different endpoints by standardizing the treatment effect (t statistics)

The standardized test statistics were used to assess the results of the primary efficacy analyses across EMERGE, and ENGAGE with the goal of evaluating **the totality of statistical evidence on efficacy**

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02484547 Accessed February 21, 2021; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477800 Accessed February 21, 2021.

The standardized test statistics:

The divergent Phase 3 primary endpoint results are challenging if evaluated in isolation

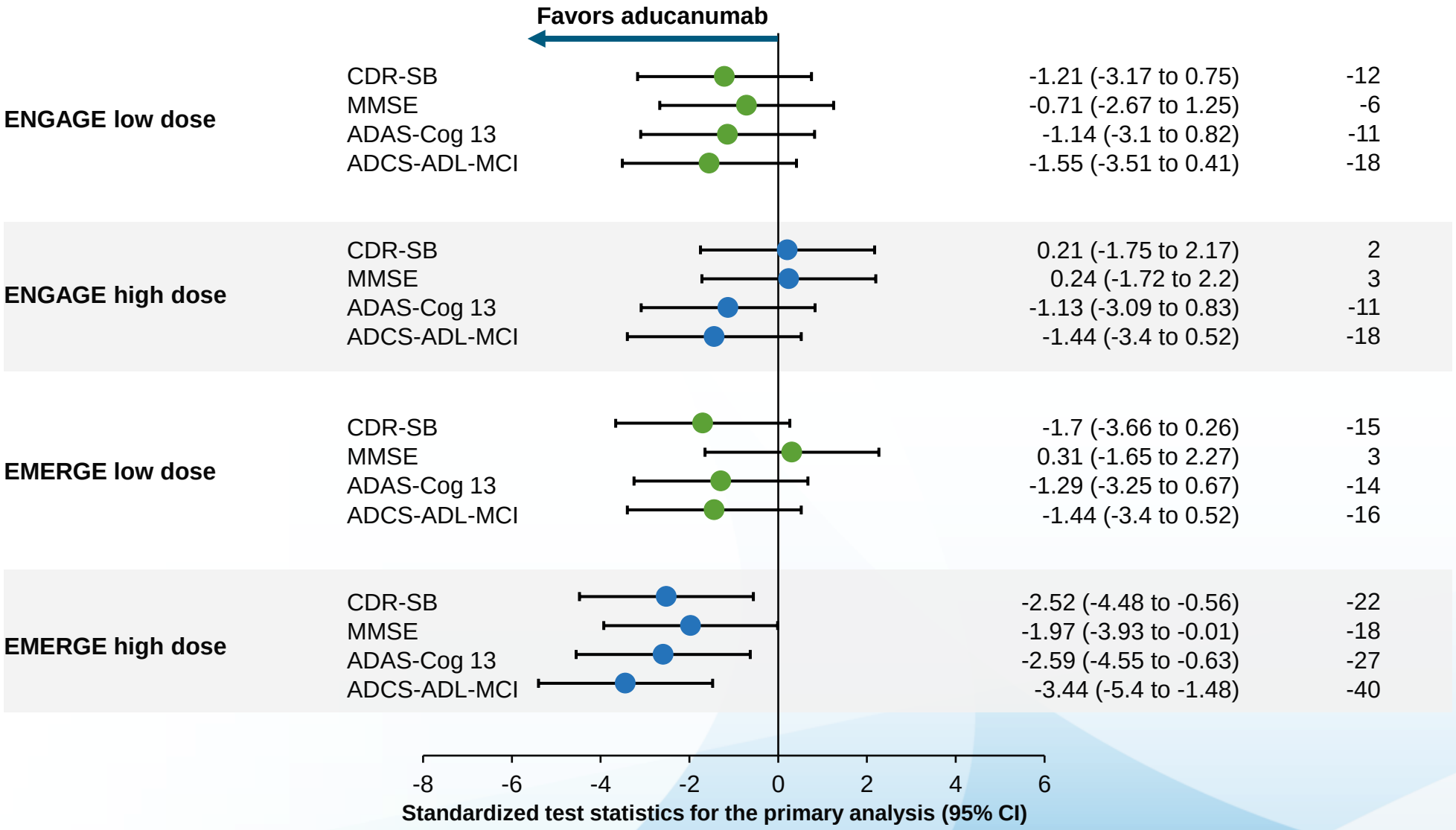


Results for CDR-SB were based on an MMRM, with change from baseline CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. The change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI scores were also analyzed using MMRM.

AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination;

The standardized test statistics:

Demonstrated consistency in the totality of statistical evidence from aducanumab clinical studies



A correlation of 0.3 to 0.5 was observed between endpoints.
Results for CDR-SB were based on an MMRM, with change from baseline CDR-SB as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region, and laboratory ApoE status. The change from baseline in MMSE, ADAS-Cog 13 and ADCS-ADL-MCI scores were also analyzed using MMRM.
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Statistical methodologies and objectives[1,2]

The **global statistical test (GST)[3]** assesses the totality of the evidence of multiple scales by standardizing all endpoints and combining them into a single univariate scale

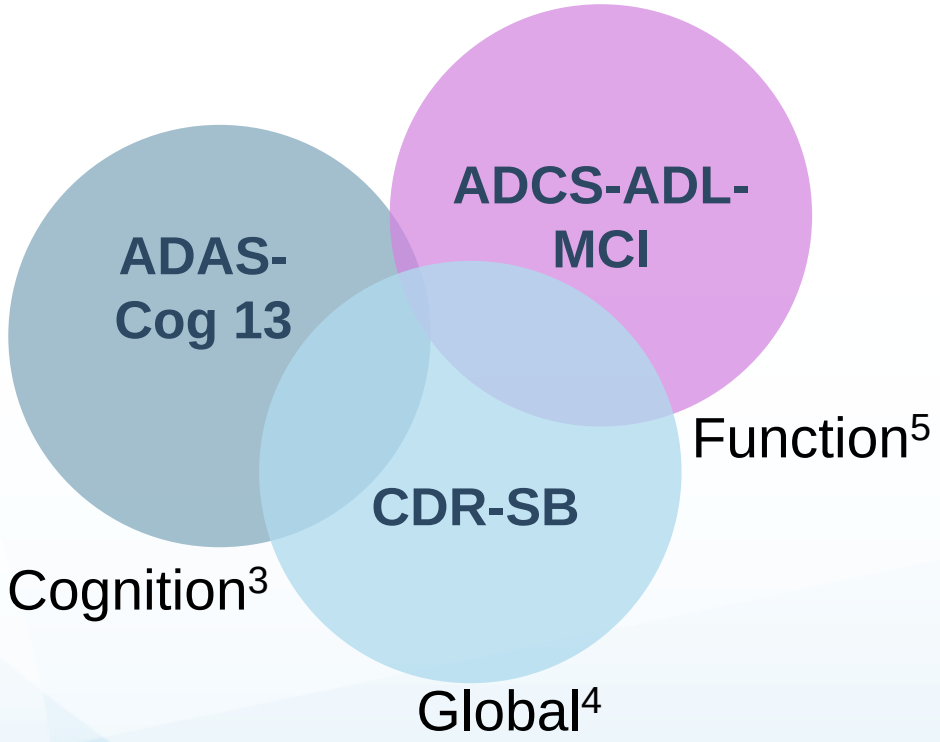
The GST assesses **the overall treatment effect of aducanumab in EMERGE and ENGAGE** across 3 clinical endpoints (CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI) by averaging the standardized *z* scores

ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; GST, global statistical test.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02484547 Accessed February 21, 2021; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477800 Accessed February 21, 2021; 3. O'Brien PC. *Biometrics*. 1984;40(4):1079-1087.

Global statistical test (GST)

- To capture heterogeneous clinical manifestations of Alzheimer's disease, 3 clinical endpoints were chosen for the present analysis (post hoc)
  - Primary endpoint and 2 secondary endpoints
  - MMSE was excluded to avoid double-counting cognition
- These endpoints measure distinct elements with very little overlap
- The GST is a clinically meaningful approach to demonstrate an overall drug effect on Alzheimer's disease progression
  - The GST combines outcomes to assess the overall impact of treatments in AD, highlighting the consistency of the different assessments (e.g., ADCS-ADL, ADAS-Cog, and CDR-SB)[1,2]



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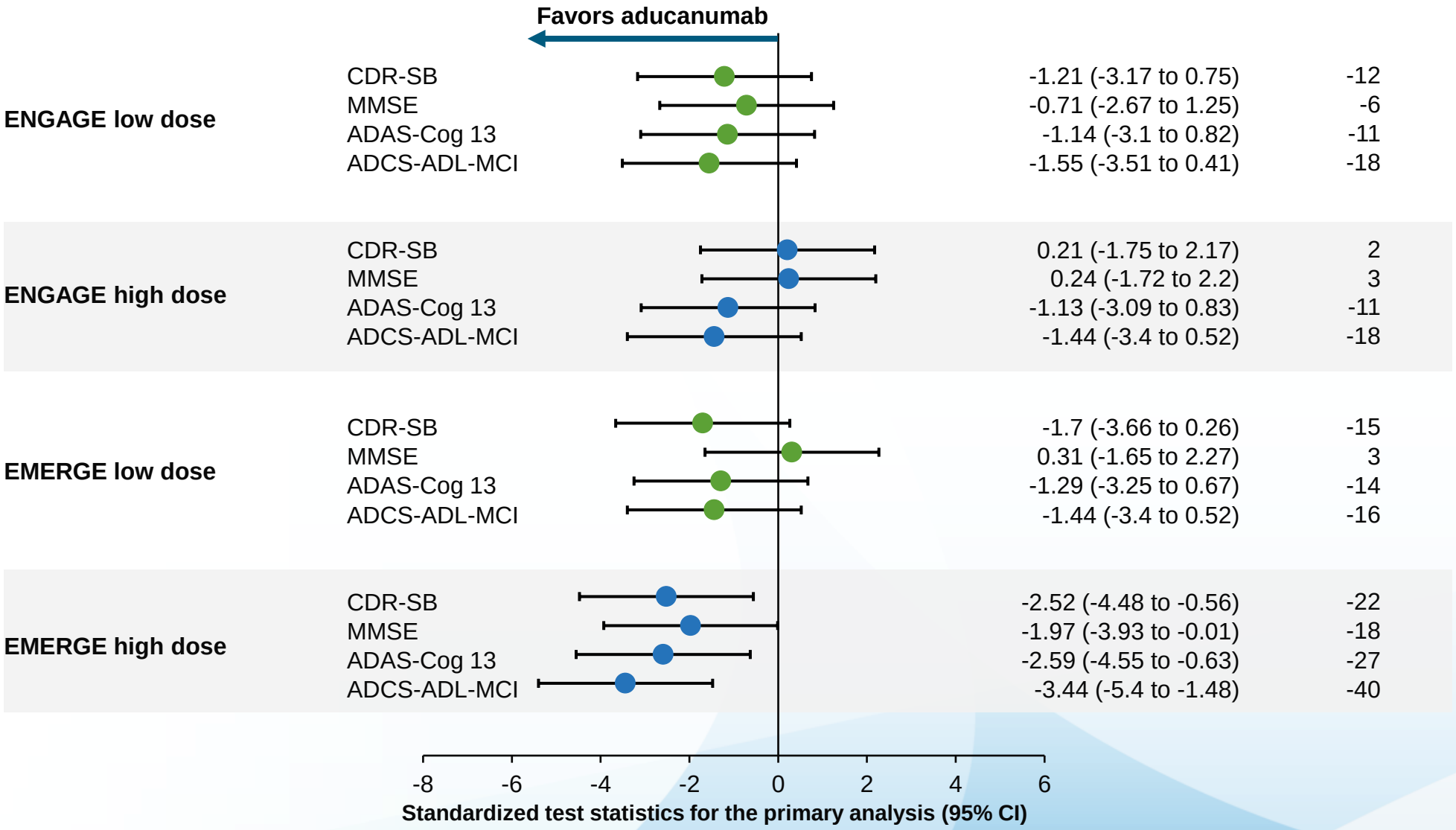
1. Boada M, et al. *Alzheimers Dement*. 2020;16(10):1412-1425; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04488419 Accessed February 8, 2021; 3. Kueper JK, et al. *J Alzheimers Dis*. 2018;63(2):423-444; 4. Cedarbaum JM, et al. *Alzheimers Dement*. 2013;9(1 suppl):S45-S55; 5. Pedrosa H, et al. *J Nutr Health Aging*. 2010;14(8):703-709.

The standardized test statistics:

Demonstrated consistency in the totality of statistical evidence from aducanumab clinical studies



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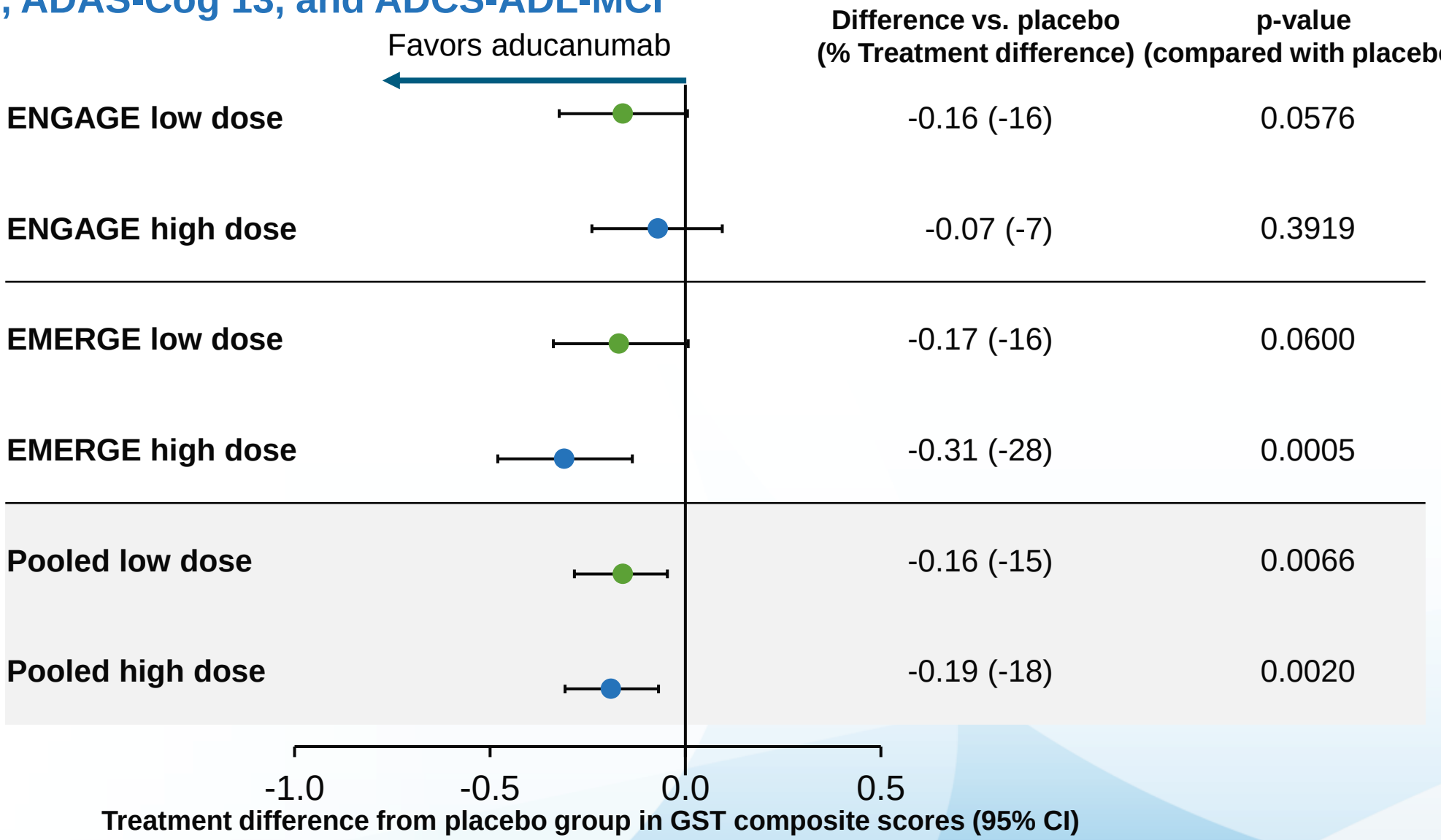
The global statistical test (GST):

CDR-SB, ADAS-Cog 13, and ADCS-ADL-MCI



Results were based on an MMRM, with change from baseline in *z* score as dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline *z* score, baseline *z* score by visit interaction, baseline MMSE *z* score, AD symptomatic medication use at baseline, region, and laboratory ApoE status.

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Standardized test statistics and GSTs demonstrate consistency in the totality of statistical evidence from aducanumab across efficacy endpoints in EMERGE and ENGAGE

- Statistical approaches further demonstrated a treatment benefit with aducanumab in early Alzheimer's disease
  - Standardized test statistics demonstrated a positive treatment effect with aducanumab across efficacy endpoints in EMERGE and ENGAGE
  - The GST supported positive overall effects of aducanumab across cognition, function, and global performance
    - EMERGE had a statistically significant overall treatment effect over placebo
    - ENGAGE had a numeric advantage over placebo
    - Low-dose groups also showed a numeric advantage over placebo
- Overall statistical evidence supports an aducanumab treatment effect in patients with early Alzheimer's disease

GST, global statistical test.

EMERGE and ENGAGE results are not due to chance

- Statistical evidence is strong across phase 3 studies and both doses
- Clinical meaningfulness and safety should be considered separately
- Alzheimer’s disease clinical trials leave little room for error and benefit from assessing the totality of statistical evidence
- Dismissing the totality of statistical evidence of effect in EMERGE and ENGAGE sets a bad precedent for the field

GST, global statistical test.

Acknowledgments

We thank the Alzheimer’s disease community, all the patients and their family members participating in the aducanumab studies, and the investigators and their staff conducting these studies