Heterogeneity in Symptom Progression and Treatment Response: An Analysis of Participants With Early Alzheimer's Disease From the EMERGE Aducanumab Trial

Sharon Cohen,[1] Jennifer Murphy,[2] John Harrison,[3-5] Judith Jaeger,[6,7] Lili Yang,[2] Shuang Wu,[2] Ping He,[2] Carmen Castrillo-Viguera,[2] Samantha Budd Haeberlein[2]

1. Toronto Memory Program, Toronto, ON, Canada
2. Biogen, Cambridge, MA, USA
3. Alzheimercentrum, AUmC, Amsterdam, The Netherlands
4. Metis Cognition Ltd, Wiltshire, UK
5. Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
6. CognitionMetrics, LLC, CT, USA
7. Albert Einstein College of Medicine, NY, USA

AD/PD 2022, Barcelona, Spain

March 15-20, 2022

Disclosures

- SC reports consulting fees (no personal fees) from Alnylam, Biogen, Cogstate, Cassava Neurosciences, Eisai, Eli Lilly, Inmune Bio, ProMIS Neurosciences, RetiSpec, Roche. She also reports research grants (paid to institution from AgeneBio, Alector, Alnylam, Anavex, Biogen, Cassava Neurosciences, Eisai, Eli Lilly, Green Valley, Janssen, NovoNordisk, RetiSpec, Roche, UCB Biopharma, Vielight
- JH reports receipt of personal fees in the past 2 years from Actinogen, AlzeCure, Aptinyx, Astra Zeneca, Athira Therapeutics, Axoltis, Axon Neuroscience, Axovant, Bial Biotech, Biogen Idec, BlackThornRx, Boehringer Ingelheim, Brands2life, Cerecin, Cognito, Cognition Therapeutics, Compass Pathways, Corlieve, Curasen, EIP Pharma, Eisai, G4X Discovery, GfHEU, Heptares, ImPACT, Ki Elements, LSP Operations, Lundbeck, Lysosome Therapeutics, MyCognition, Neurocentria, Neurocog, Neurodyn Inc, Neurotrack, the NHS, Novartis, Novo Nordisk, Nutricia, Probiodrug, Prothena, Recognify, Regeneron, reMYND, Rodin Therapeutics, Samumed, Sanofi, Signant, Syndesi Therapeutics, Takeda, Vivoryon Therapeutics and Winterlight Labs. Additionally, he holds stock options in Neurotrack Inc. and is a joint holder of patents with My Cognition Ltd.
- JJ is president and owner of CognitionMetrics, LLC which has provided paid consulting services to the following companies over the past two years: Alkermes, Ovid, Jazz, Biogen, Jannsen, INmuneBio, Lundbeck, Syndesi, Cumulus, Eisai, Umecrine, Shackelford, Cyclerion. Additionally she serves on the Board of Apex and is a holder of stock options in InmuneBio.
- JM, SW, PH, CCV, and SBH are employees and shareholders of Biogen
- LY was an employee of Biogen at the time of this work and have since left the company
- 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

Introduction

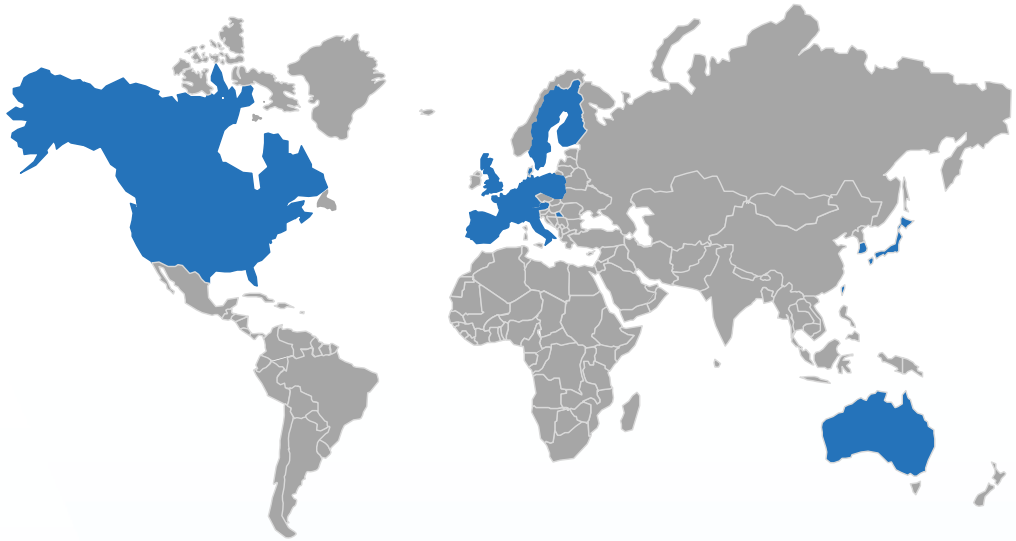
- Aducanumab is a human, immunoglobulin gamma 1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ[1]
- Aducanumab is the first FDA-approved Alzheimer's disease (AD) treatment that reduces Aβ plaques, a defining pathophysiological feature of AD[2]
- Two randomized clinical trials, EMERGE (NCT02484547) and ENGAGE (NCT02477800) were conducted in 3285 patients with early AD[3,4]
- EMERGE demonstrated a statistically significant difference between drug and placebo in the prespecified primary and secondary clinical endpoints[2]
- A previously-presented item-level analysis of EMERGE showed consistent aducanumab treatment effects across cognitive, functional, and behavioral domains in early AD[5]
- Differences in progression and treatment response between participants at the MCI vs. the mild AD dementia stage of AD have not been presented to date

Aβ, amyloid beta; FDA, US Food and Drug Administration; MCI, mild cognitive impairment.

1. Sevigny J, et al. *Nature.* 2016; 537(7618):50-56; 2. Aduhelm (aducanumab). Prescribing information. Biogen, Inc.; 2021; 3. ClinicalTrials.gov. Accessed February 10, 2022. https://clinicaltrials.gov/ct2/show/NCT02484547; 4. ClinicalTrials.gov. Accessed February 10, 2022. https://clinicaltrials.gov/ct2/show/NCT02477800; 5. Cohen S, et al. AAIC 2021.

Aducanumab Phase 3 studies EMERGE and ENGAGE

Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease • MCI due to Alzheimer's disease (n=1336) + mild Alzheimer's disease dementia (n=302) • MMSE 24-30, CDR-GS 0.5, RBANS DMI score ≤ 85 • Confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high dose) and placebo; randomized 1:1:1
Primary endpoint	▪ Change from baseline in CDR-SB score at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Tertiary (efficacy): NPI-10 ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers



Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

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-GS, Clinical Dementia Rating Scale–Global; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10-item); PET, positron-emission tomography; RBANS DMI, Repeatable Battery for Assessment of Neuropsychological Status–Delayed Memory Index.

1. ClinicalTrials.gov. Accessed February 10, 2022. https://clinicaltrials.gov/ct2/show/NCT02484547; 2. ClinicalTrials.gov. Accessed February 10, 2022. https://clinicaltrials.gov/ct2/show/NCT02477800.

Objectives

- To compare the clinical symptom profiles of EMERGE participants with mild cognitive impairment due to AD versus those with mild AD dementia
- To examine the pattern of aducanumab treatment response in EMERGE participants with mild cognitive impairment due to AD vs. those with mild AD dementia

AD, Alzheimer’s disease.

Methods

- EMERGE data were analyzed (ENGAGE did not meet the primary endpoint)
- EMERGE (N=1643) included participants aged 50-85 years with confirmed presence of amyloid pathology and mild cognitive impairment or mild AD dementia, consistent with Stage 3 and Stage 4 Alzheimer's disease[1]
- Aducanumab or placebo was administered via intravenous infusion every 4 weeks over 76 weeks (20 doses total); details of the trial design, patient population, and futility analysis have been disclosed[2]
- Participants were randomized to receive high-dose aducanumab, low-dose aducanumab, or placebo
- The primary endpoint was change from baseline in CDR-SB score at Week 78. Secondary outcome measures were MMSE, ADAS-Cog13, and ADCS-ADL-MCI scores. NPI-10 was a tertiary clinical outcome measure
- Item-level analyses using mixed models for repeated measures were conducted on these clinical efficacy endpoints using the ITT population. This analysis is considered descriptive; thus, no multiplicity adjustment was considered
- Item-level analyses of symptom progression in the placebo group and treatment differences between placebo and high-dose aducanumab were analyzed separately for ADAS-Cog 13 and ADCS-ADL-MCI. Separate analyses were conducted for participants with MCI due to AD (n=1336) or mild AD dementia (n=302)

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

1.US Food and Drug Administration. Early Alzheimer's disease: developing drugs for treatment guidance for industry. 2018. Accessed June 4, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industry.

Baseline demographics from EMERGE

	MCI due to AD				Mild AD dementia			
	Placebo (n=446)	Low dose aducanumab (n=452)	High dose aducanumab (n=438)	Total (n=1336)	Placebo (n=102)	Low dose aducanumab (n=91)	High dose aducanumab (n=109)	Total (n=302)
Age, mean, years	70.8	70.6	70.8	70.7	70.9	70.7	69.9	70.5
Sex, n (%)								
Female	242 (54.3)	220 (48.7)	228 (52.1)	690 (51.6)	48 (47.1)	49 (53.8)	56 (51.4)	153 (50.7)
Male	204 (45.7)	232 (51.3)	210 (47.9)	646 (48.4)	54 (52.9)	42 (46.2)	53 (48.6)	149 (49.3)
Race, n (%)								
American Indian or Alaska native	1 (0.2)	0	0	1 (<0.1)	0	0	0	0
Asian	36 (8.1)	32 (7.1)	25 (5.7)	93 (7.0)	11 (10.8)	7 (7.7)	17 (15.6)	35 (11.6)
Black or African American	0	6 (1.3)	4 (0.9)	10 (0.7)	1 (1.0)	0	0	1 (0.3)
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0	0	0
White	354 (79.4)	360 (79.6)	349 (79.7)	1063 (79.6)	77 (75.5)	72 (79.1)	73 (67.0)	222 (73.5)
Not reported	54 (12.1)	53 (11.7)	58 (13.2)	165 (12.4)	13 (12.7)	12 (13.2)	17 (15.6)	42 (13.9)
Other	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)	0	0	2 (1.8)	2 (0.7)
Unknown	0	0	1 (0.2)	1 (<0.1)	0	0	0	0
Years of formal education, mean	14.6	14.5	14.6	14.6	14.1	14.5	14.0	14.2

- Age, sex, education, and racial characteristics were well balanced across the MCI group and the mild AD dementia group

ADCS-ADL-MCI, the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI.

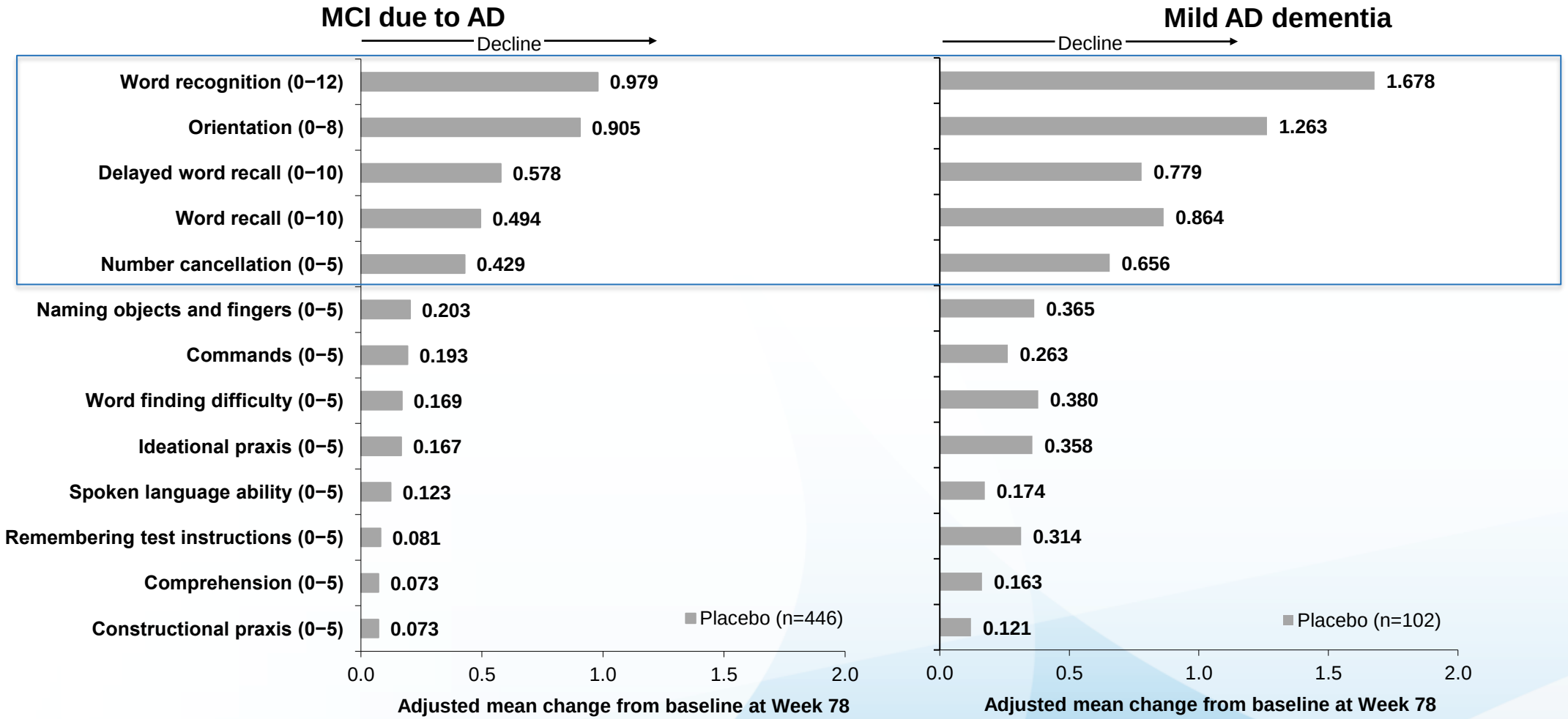
Baseline disease characteristics from EMERGE

	MCI due to AD				Mild AD dementia			
Characteristic, n (%)	Placebo (n=446)	Low dose aducanumab (n=452)	High dose aducanumab (n=438)	Total (n=1336)	Placebo (n=102)	Low dose aducanumab (n=91)	High dose aducanumab (n=109)	Total (n=302)
Laboratory ApoE e4 status								
Carrier	299 (67.0)	310 (68.6)	294 (67.1)	903 (67.6)	69 (67.6)	52 (57.1)	71 (65.1)	192 (63.6)
Non-carrier	146 (32.7)	140 (31.0)	144 (32.9)	430 (32.2)	32 (31.4)	38 (41.8)	37 (33.9)	107 (35.4)
RBANS delayed memory index score, mean	61.3	60.4	61.6	61.1	56.8	58.0	57.0	57.3
CDR sum of boxes, mean	2.38	2.40	2.40	2.39	2.85	2.80	2.93	2.86
MMSE, mean	26.5	26.3	26.4	26.4	25.9	25.9	25.9	25.9
ADAS-Cog 13, mean	21.213	22.020	21.626	21.622	24.709	24.817	24.759	24.760
ADCS-ADL-MCI, mean	42.9	43.0	43.0	43.0	41.6	41.5	40.5	41.2
Years since diagnosis of AD, mean	1.23	1.21	1.23	1.22	1.49	1.44	1.50	1.48
Participants taking any AD symptomatic medication at baseline	214 (48.0)	214 (47.3)	198 (45.2)	626 (46.9)	68 (66.7)	67 (73.6)	87 (79.8)	222 (73.5)

- Across treatment groups and disease stages, the majority of participants were ApoE e4 carriers
- Mean CDR-SB at baseline was 2.39 in the MCI due to AD group and 2.86 in the mild AD dementia group
- 46.9% of patients with MCI due to AD vs. 73.5% of patients with Mild AD dementia were taking AD symptomatic medication at baseline

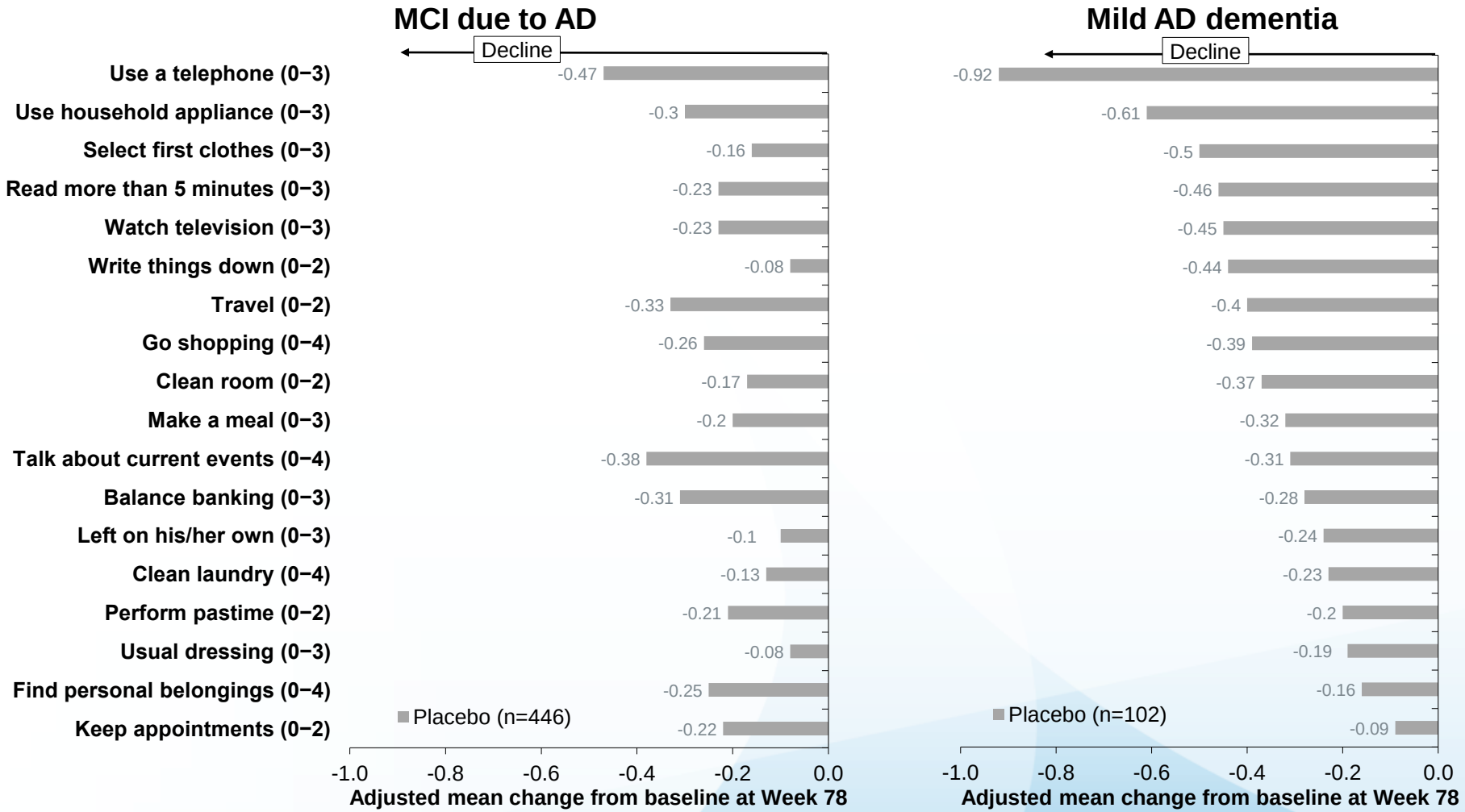
AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL-MCI, the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI; ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

In the placebo group, larger decline in ADAS-Cog13 domains over 78 weeks was observed in mild AD dementia



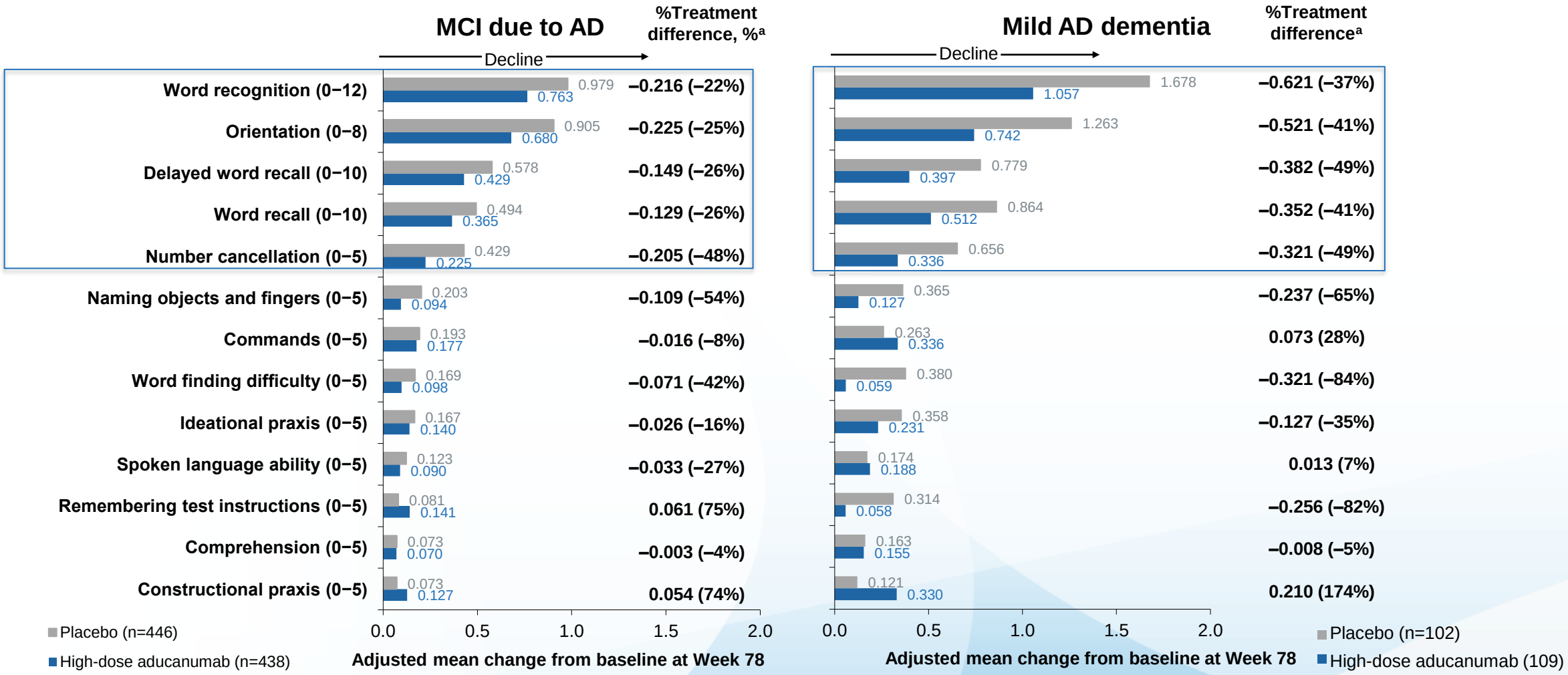
Results were based on an MMRM, with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline item value, baseline item score by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region and laboratory ApoE status. All three treatment groups were included in the model. AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive subscale; ApoE, apolipoprotein E; MCI, mild cognitive impairment; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination.

Variable declines in ADCS-ADL-MCI items over 78 weeks in MCI due to AD; all items progressed in mild AD dementia



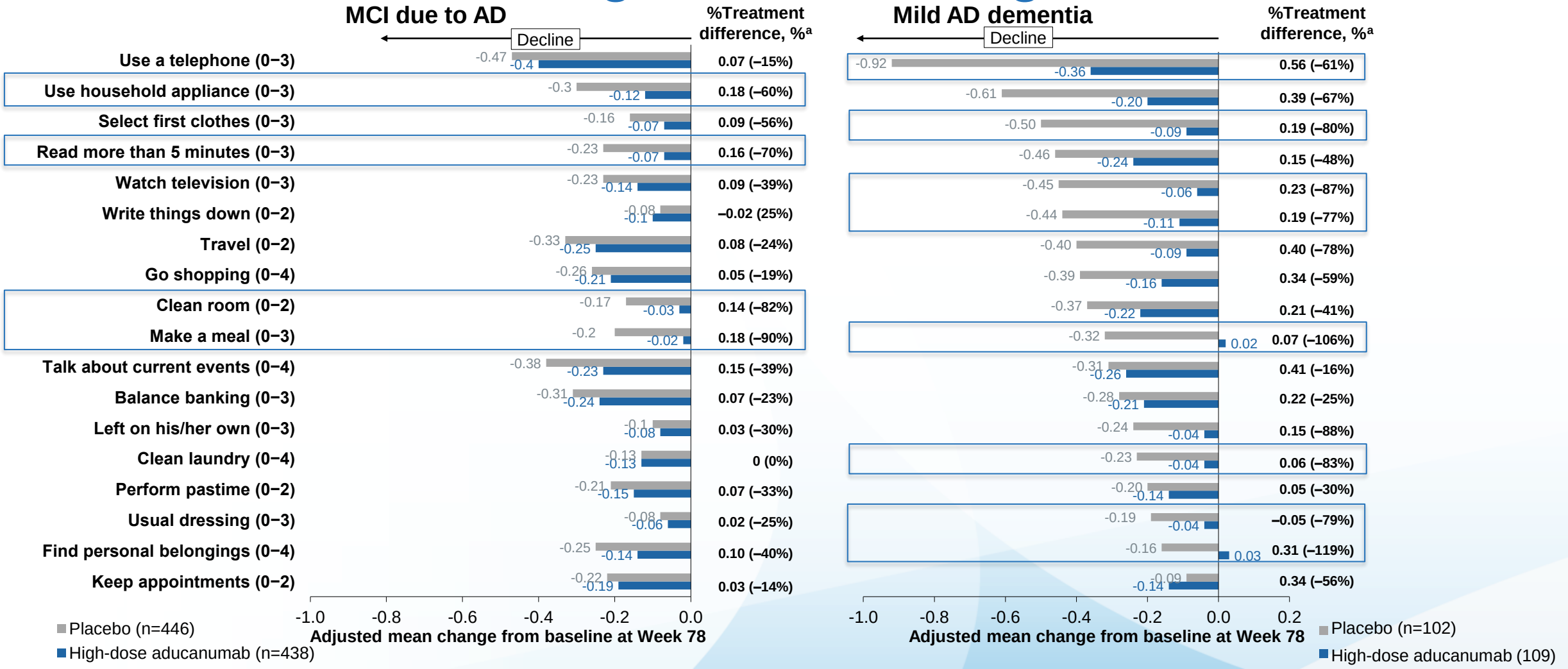
Results were based on an MMRM, with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline item value, baseline item score by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region and laboratory ApoE status. All three treatment groups were included in the model. AD, Alzheimer's disease; ADCS-ADL MCI, the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI; ApoE, apolipoprotein E; MCI, mild cognitive impairment; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination.

Treatment differences over 78 weeks on the ADAS-Cog13 differed according to disease stage



[a] Results were based on an MMRM, with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline item value, baseline item score by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region and laboratory ApoE status. All three treatment groups were included in the model. AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive subscale; ApoE, apolipoprotein E; MCI, mild cognitive impairment; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination.

Treatment difference over 78 weeks on the ADCS-ADL-MCI differed according to disease stage



[a] Results were based on an MMRM, with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline item value, baseline item score by visit interaction, baseline MMSE, AD symptomatic medication use at baseline, region and laboratory ApoE status. All three treatment groups were included in the model. AD, Alzheimer's disease; ADCS-ADL MCI, the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI; ApoE, apolipoprotein E; MCI, mild cognitive impairment; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination.

Conclusions

- Based on data from placebo-treated patients with MCI due to AD and mild AD dementia in EMERGE, the clinical progression of Alzheimer's disease follows the expected pattern and exhibits different patterns for different baseline clinical stages
    - Patients with MCI due to AD demonstrate decline in memory, orientation, and activities of daily living, but the most demanding cognitive skills and most complex activities of daily living stand out as the most measurable in this early-stage
    - At the mild AD dementia stage, a broader array of cognitive deficits are measurable, along with decline in the ability to independently perform simpler activities of daily living
- Treatment effects with aducanumab were observed in both the MCI and mild AD dementia stages of the disease
- Treatment effects were most evident on the specific individual items most affected by patients in the early stages of AD
    - On the ADAS-Cog 13, patients with MCI due to AD and mild AD dementia benefited from maintaining executive functioning, memory, and orientation skills. The MCI group stood out in terms of having twice the measurable treatment effect on the single executive functioning test, Number Cancellation
    - On the ADCS-ADL-MCI, at the MCI stage, patients' treatment benefits are seen in more complex activities that require judgment and concentration. At the mild AD dementia stage, simpler activities such as dressing are beneficially impacted by treatment
- Treating AD in its earliest symptomatic stages of MCI and mild AD dementia helps preserve complex cognitive processing and independence in high-level functional activities
- Larger treatment effects in the mild AD dementia stage reflect the opportunity to preserve remaining cognitive and functional abilities
- Interpretation of these analyses is limited by the small sample size of the mild AD dementia group

AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL-MCI, the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI; ADL, activities of daily living; MCI, mild cognitive impairment.

Acknowledgments

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