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Item-Level Analysis of Clinical Measures in Patients With Early Symptomatic Alzheimer's Disease Following Treatment With High-Dose Aducanumab in the Phase 3 Study EMERGE

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OBJECTIVE

- To examine the treatment benefit of high-dose aducanumab across individual items/domains in the primary, secondary, and tertiary clinical endpoints in EMERGE.

CONCLUSIONS

- The item-level analyses are consistent with the results from the primary analysis of the clinical endpoints.
- The aducanumab high-dose group showed a consistent drug-placebo difference across 5 clinical efficacy endpoints, slowing clinical decline over 78 weeks.
- The results demonstrate the consistency of the aducanumab treatment effect in slowing decline across cognitive, functional, and behavioral domains in early Alzheimer's disease.

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 treatment that reduces Aβ plaques, a defining pathophysiological feature of Alzheimer's disease.[2]
- The efficacy of aducanumab was evaluated in two Phase 3, double-blind, randomized, placebo-controlled, parallel group studies in patients with Alzheimer's disease (EMERGE, NCT02484547 and ENGAGE, NCT02477800). EMERGE and ENGAGE were terminated prior to their planned completion; study endpoints were analyzed based on the prespecified statistical analysis plan. The effects of aducanumab were supported by a Phase 1b, double-blind, randomized, placebo-controlled, dose-ranging study (PRIME, NCT01677572).[2]
- EMERGE demonstrated a statistically significant drug-placebo difference in the prespecified primary and secondary clinical endpoints.[2]
- This analysis tested the consistency of aducanumab treatment effects across multiple domains within clinical assessments.

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 dementia, consistent with Stage 3 and Stage 4 Alzheimer's disease.[3]
- Aducanumab or placebo was administered via intravenous infusion every 4 weeks over 76 weeks (20 doses total); details on the trial design, patient population, and futility analysis have been disclosed.[4]
- Participants were randomized to receive high-dose aducanumab, low-dose aducanumab, or placebo. Baseline characteristics are shown in **Table 1**.
- 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 model for repeated measures were conducted on these clinical efficacy endpoints using the ITT population. Due to deviation from the normality assumption, this analysis is considered descriptive and, thus, no multiplicity adjustment was considered.

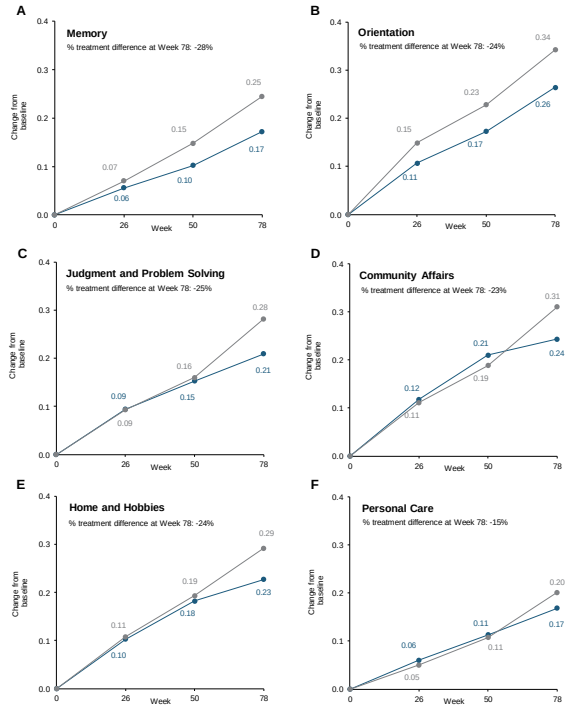
Table 1. Demographic and baseline disease characteristics

	Placebo (n=548)	High dose aducanumab (n=547)
Age in years, mean ± SD	70.8±7.4	70.6±7.5
Female, n (%)	290 (53)	284 (52)
Race, n (%)		
Asian	47 (9)	42 (8)
White	431 (79)	422 (77)
Education years, mean ± SD	14.5±3.7	14.5±3.6
Alzheimer's disease medications used, n (%)	282 (51)	285 (52)
ApoE ε4, n (%)		
Carriers	368 (67)	365 (67)
Noncarriers	178 (32)	181 (33)
Clinical stage, n (%)		
MCI due to Alzheimer's disease	446 (81)	438 (80)
Mild Alzheimer's disease	102 (19)	109 (20)
RBANS delayed memory score, mean ± SD	60.5±14.2	60.7±14.2
CDR global score, n (%)		
0.5	545 (99)	546 (>99)
1	3 (1)	1 (<1)
CDR-SB score, mean ± SD	2.47±1.00	2.51±1.05
MMSE score, mean ± SD	26.4±1.8	26.3±1.7
ADAS-Cog 13 score, mean ± SD	21.87±6.73	22.25±7.07
ADCS-ADL-MCI score, mean ± SD	42.6±5.7	42.5±5.8
NPI-10 score, mean ± SD	4.3±5.9	4.5±6.38

Results

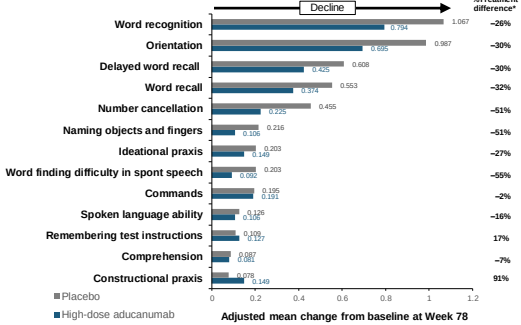
- At Week 78, treatment effects were observed across all 6 domains of the CDR (**Figure 1**).
- An aducanumab treatment effect was evident by slowing of decline on the ADAS-Cog13 items that are sensitive to change in early symptomatic Alzheimer's disease (e.g., word recognition, orientation, word recall [immediate and delayed], and number cancellation) (**Figure 2**).
- The clinical benefit of aducanumab with respect to preserving daily function was observed across a broad range of items on the ADCS-ADL-MCI (**Figure 3**).
- Aducanumab treatment was associated with a reduction in the behavioral and psychiatric symptoms associated with Alzheimer's disease, as measured by NPI-10 (**Figure 4**).

Figure 1. Longitudinal change in each CDR domain*



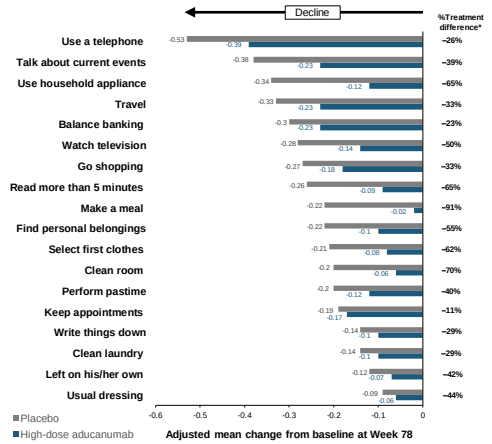
*A negative % treatment difference indicates less disease progression.

Figure 2. ADAS-Cog13 item change at Week 78



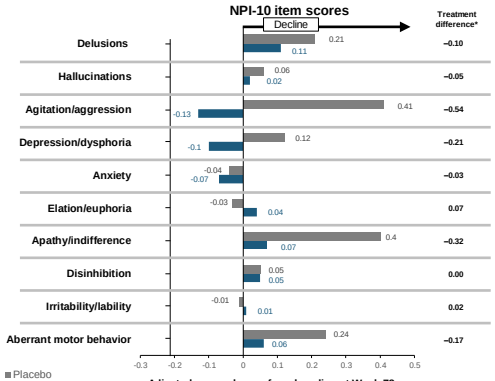
*A negative % treatment difference indicates less disease progression.

Figure 3. ADCS-ADL-MCI item change at Week 78



*A negative % treatment difference indicates less disease progression.

Figure 4. NPI-10 item change at Week 78



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Abbreviations Aβ, amyloid beta; ADAS-Cog13, Alzheimer's Disease Assessment Scale cognitive subscale 13 items; ADCS-ADL-MCI, the Alzheimer's Disease Cooperative Study-Activities of Daily Living-MCI; ApoE ε4, apolipoprotein E ε4; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating Sum of Boxes; FDA, US Food and Drug Administration; ITT, intention-to-treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NCT, National Clinical Trial; NPI-10, 10-item Neuropsychiatric Inventory Questionnaire; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status. References 1. Sevigny J, et al. *Nature* 2016; 537(7618):50-6; 2. Aduhelm. Prescribing information. Biogen, Inc.; 2021; 3. FDA. Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry. 2018. In. Guidance Compliance Regulatory Information 2018. 4. Combined FDA and applicant PCNS Drugs Advisory Committee briefing document. US Food and Drug Administration website. Published November 6, 2020. Accessed 4 June 2021. Disclosures PH, MLB, RM, FF, MP, CCV, YT, LY, and SBH are employees and shareholders of Biogen. SC was an ENGAGE trial site investigator and an Aducanumab Steering Committee member. She is a consultant to Biogen, Cassava Sciences, Cognstate, Ilhmune Bio, ProMIS Neuroscience, and RetiSpec (no personal fees) and receives research support (paid to institution) from AgeneBio, Anavex, Biogen, Cassava Sciences, Eisai, Genentech, Eli Lilly, Janssen, RetiSpec, Roche, and Velight. JH has received personal fees in the past 2 years from AlzeCure, Aptinyx, Astra Zeneca, Athira Therapeutics, Axon Neuroscience, Axovant, Biogen Idec, BlackThornRx, Boehringer Ingelheim, Cerecin, Cognition Therapeutics, Compass Pathways, CRF Health, Curasen, EIP Pharma, Eisai, Eli Lilly, FSV7, G4X Discovery, GfHEU, Heptares, Lundbeck, Lysosome Therapeutics, MyCognition, Neurocentria, Neurocog, Neurodyn Inc, Neurotrack, Novartis, Nutricia, Probiodrug, Regeneron, Rodin Therapeutics, Samumed, Sanofi, Servier, Signant, Syndesi Therapeutics, Takeda, Vivoryon Therapeutics, vTv Therapeutics, and Winterlight Labs. He holds stock options in Neurotrack Inc. and is a joint holder of patents with My Cognition Ltd. JJ is the owner and President of CognitionMetrics, LLC which received fees from Biogen in consideration of scientific consulting services. CJM was an ENGAGE trial site investigator and an Aducanumab Steering Committee member. She is supported by NIHR Biomedical Research Centre at UCLH and has acted as a consultant to Biogen, Roche, and IONIS. AP reports personal fees from Acadia Pharmaceuticals, Avanir, Cadent Therapeutics, Functional Neuromodulation, Synexs, and BioXcel, and grants to his institution from Avanir, Biogen, Biohaven, Eisai, Eli Lilly, Genentech/Roche, and Novartis. JC has provided consultation to Acadia, Actinogen, Acumen, Alector, Alkahest, Alzheon, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, Cytox, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Merck, Novo Nordisk, Otsuka, ReMYND, Resverlogix, Roche, Samumed, Samus, Signant Health, Sunovion, Suven, and United Neuroscience pharmaceutical and assessment companies. He has stock options in ADAMAS, AnnovisBio, MedAvante, and BiOasis. He owns the copyright of the Neuropsychiatric Inventory. . JTP received honoraria from Avanair, Biogen, Genzyme, Novartis, and Teva and research support from Biogen and Roche. KJP served on advisory boards for Bayer, Biogen, BPL, Octapharma, and Pfizer and received educational support and travel grants from Biogen, Novo Nordisk, Octapharma, and Pfizer. Acknowledgments This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Meditech Media (Atlanta, GA, USA): funding was provided by Biogen.