GRADUATE I GRADUATE II

GRADUATE I and II: Topline Results of Two Global, Phase III, Randomized, Placebo-Controlled Studies Assessing the Efficacy and Safety of Subcutaneous Gantenerumab in Early Alzheimer's Disease

Randall J Bateman, MD, PhD[1], Janice Smith, PhD[2], Michael C Donohue, PhD[3], Paul Delmar, PhD[4], Rachid Abbas, MD, PhD[4], Stephen Salloway, MD, PhD[5], Jakub Wojtowicz, MPharm[4], Kaj Blennow, PhD[6,7], Tobias Bittner, PhD[4,8], Sandra E Black, MD, FRCPC[9,10], Gregory Klein, PhD[4], Mercè Boada, MD[11], Timo Grimmer, MD[12], Akira Tamaoka, MD, PhD[13], Richard J Perry, MD[14], R Scott Turner, MD, PhD[15], David Watson, PsyD[16], Michael Woodward, MD[17], Angeliki Thanasopoulou, PhD[4], Christopher Lane, MD, PhD[2], Monika Baudler-Klein, PhD[4], Nick C Fox, MD[18,19], Jeffrey L Cummings, MD, ScD[20], Paulo Fontoura, MD[4], Rachelle S Doody, MD, PhD[4,8] for the GRADUATE I and GRADUATE II Clinical Investigators and the Gantenerumab Study Group

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Affiliations

1. Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA
2. Roche Products Ltd, Welwyn Garden City, UK
3. Alzheimer's Therapeutic Research Institute, Keck School of Medicine, University of Southern California, San Diego, CA, USA
4. F. Hoffmann-La Roche Ltd, Basel, Switzerland
5. Butler Hospital and Warren Alpert Medical School of Brown University, Providence, RI, USA
6. Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden
7. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
8. Genentech, Inc., South San Francisco, CA, USA
9. Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
10. LC Campbell Cognitive Neurology Research Unit, Dr Sandra Black Centre for Brain Resilience and Recovery, Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada
11. Ace Alzheimer Center Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain
12. Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany
13. Department of Neurology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
14. Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, UK
15. Department of Neurology, Georgetown University School of Medicine, Washington DC, USA
16. Alzheimer's Research and Treatment Center, Wellington, FL, USA
17. Medical and Cognitive Research Unit, Heidelberg Repatriation Hospital, Austin Health, Melbourne, VIC, Australia
18. Dementia Research Centre, Department of Neurodegenerative Disease, Queen Square Institute of Neurology, University College London, London, UK
19. UK Dementia Research Institute, Queen Square Institute of Neurology, University College London, London, UK
20. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, NV, USA

Disclosures

- **Randall J Bateman** is a co-founder and on the scientific advisory board of C2N Diagnostics and reports research support from AbbVie, Avid Radiopharmaceuticals, Biogen, Bristol Meyers Squibb, Centene, Eisai, Eli Lilly and Company, Genentech, Inc., F. Hoffmann-La Roche Ltd, Janssen, and Novartis. He has provided consulting services for Amgen and F. Hoffmann-La Roche
- **Janice Smith** and **Christopher Lane** are employees of Roche Products Ltd and own stocks or stock options in F. Hoffmann-La Roche Ltd
- **Paul Delmar, Rachid Abbas, Jakub Wojtowicz, Tobias Bittner, Gregory Klein, Angeliki Thanasopoulou, Monika Baudler-Klein, Paulo Fontoura,** and **Rachelle S Doody** are employees of F. Hoffmann-La Roche Ltd and own stocks or stock options in F. Hoffmann-La Roche Ltd
- **Tobias Bittner** and **Rachelle S Doody** are employees of Genentech, Inc., part of F. Hoffmann-La Roche Ltd
- **Michael C Donohue** reports consulting fees from Roche. He serves on the data monitoring committee for KeifeRx, the scientific advisory board for Prothena, and his spouse is a full-time employee of Janssen
- **Stephen Salloway** was the co-chair of the investigator steering committee for the aducanumab Phase III program and he served as a site PI for the aducanumab and lecanemab Phase III studies, the donanemab Phase II trial, and he was the project arm leader for gantenerumab in DIAN-TU. He has received consulting income from Biogen, Lilly, Roche, Genentech, Inc., Bolden, Amylyx, Prothena, and Eisai. He has no stock or royalties related to any medication in development. Dr Salloway serves on the planning committee for the National Disease Modifying Treatment and Diagnostic Registry Work Group and he is a member of the ADRD Therapeutics Work Group. He is the first author for the report of ARIA in aducanumab Phase III trial (Salloway, *JAMA Neurology*, 2022), the report of gantenerumab and solanezumab in DIAN-TU (Salloway, *Nature Medicine*, 2021). He is a co-author on the report of the donanemab Phase II trial (Mintun, *NEJM*, 2021) and the aducanumab appropriate use recommendations (Cummings, *Journal of Prevention of Alzheimer's Disease*, 2021)
- **Kaj Blennow** has served as a consultant and at scientific advisory boards and/or data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program
- **Sandra E Black** reports receiving in kind research support from Avid Radiopharmaceuticals and GE Healthcare, assisting in developing the ADVANCE Program, a Canadian physician webinar series on dementia sponsored by Biogen, and has presented on neuroimaging. She has also provided *ad hoc* consulting for Biogen and F. Hoffmann-La Roche Ltd and Roche Canada. She acknowledges grant support from the Canadian Institutes of Health Research, the NIH, Leducq Foundation, Dasman Institute, Alzheimer's Drug Discovery Foundation, the Weston Foundation, the Ontario Brain Institute, Brain Canada, and the Heart and Stroke Foundation of Canada

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- **Mercè Boada** is an employee of Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya, Spain and the Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain. She has also received grants from La Caixa S.A., Grifols S.A., IMI, and ISCII outside the submitted work (paid to the institution). She has served as a consultant or provided scientific advisory board services and/or given lectures for Roche, Araclon, Biogen, Grifols, Lilly S.A., Merck Sharp & Dohme, Novo Nordisk, Cortexyme, and Zambón
- **Timo Grimmer** has received consulting fees from AbbVie, Alector, Anavex, Biogen, Eli Lilly, Functional Neuromodulation, Grifols, IQVIA, Noselab, Novo Nordisk, Nui Care, Orphazyme, Roche Diagnostics, Roche Pharma, UCB, and Vivoryon; lecture fees from Grifols, Medical Tribune, Novo Nordisk, Roche Pharma, and Schwabe; and has received grants to his institution from Roche Diagnostics
- **Akira Tamaoka** receives consulting fees from Chugai Pharmaceutical Co., Ltd
- **Richard J Perry** has received consulting fees from Roche, Eli Lilly, Biogen, Merck Sharp & Dohme, and Eisai. He has received research support from GE
- **R Scott Turner** reports research support to Georgetown University from the NIH, Alzheimer's Association, Alector, Biogen, Eisai, Janssen, Lilly, Roche/Genentech, Vaccinex, and Vivoryon. He serves on the scientific advisory board of Jupiter Neurosciences, KeifeRx, and T3D Therapeutics, and serves as a consultant to Re:Cognition Health
- **David Watson** is a National Coordinator/PI for Roche
- **Michael Woodward** has received honoraria for speaking and/or advisory board participation from Roche/Genentech, GSK, Pfizer, Biogen, Nutricia, Actinogen, and Anavex. No shares or other relevant conflicts
- **Nick C Fox** reports consulting fees from Roche/Genentech, Biogen, Lilly, and Ionis - paid to UCL. He reports serving on a data safety monitoring board for Biogen and reports research support from Lilly. He acknowledges grant support from Alzheimer's Research UK, the UK Dementia Research Institute, and the UK NIHR UCLH Biomedical Research Centre
- **Jeffrey L Cummings** has provided consultation to Acadia, Actinogen, Alkahest, Alpha Cognition, AriBio, Biogen, Cassava, Cerecin, Corium Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Inc., Green Valley, GAP Innovations, Grifols, Janssen, Karuna, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, PRODEO, Prothena, ReMYND, Resverlogix, Roche, Sage Therapeutics, Signant Health, Simcere, Sunbird Bio, Suven, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies

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the investigators, and site staff

past and present

for their time and commitment to

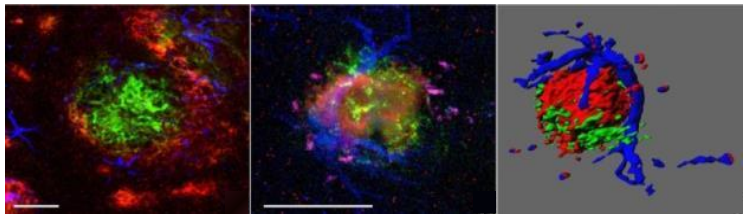
GRADUATE I and GRADUATE II

Development of subcutaneous gantenerumab, a fully human anti-Aβ monoclonal antibody targeting Alzheimer's disease[1]

Highest affinity for aggregated Aβ, including oligomers, fibrils, and plaques[2,3]

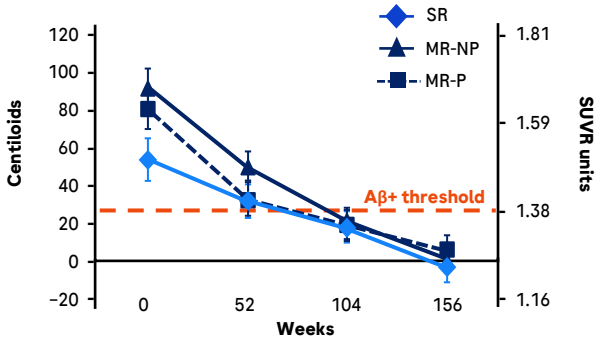
Clearance of aggregated Aβ

Microglia-mediated phagocytosis[2]



Triple labeling of microglia (blue) adjacent to gantenerumab (red) bound to Aβ deposits (green)

SR & MR OLE amyloid plaque removal[4,a]



Below positivity threshold reached by 52% of participants with a decrease of 70 CL vs baseline at Week 104

Gantenerumab has shown downstream effects on multiple biomarkers of AD pathology and neurodegeneration in clinical trials[5,6]

[a]Data from SR and MR OLE PET substudies. Aβ, amyloid-beta; AD, Alzheimer's disease; CL, centiloid; MR, Marguerite RoAD; MR-NP, Marguerite RoAD – non-placebo; MR-P, Marguerite RoAD – placebo; OLE, open-label extension; PET, positron emission tomography; SR, SCarlet RoAD; SUVR, standardized uptake value ratio.1. Doody R. J Prev Alzheimers Dis 2017;4:264–272; 2. Bohrmann B, et al. J Alzheimers Dis 2012;28:49–69; 3. Chen Y, et al. ACS Chem Neurosci 2020;11:3233–3244; 4. Klein G, et al. J Prev Alzheimers Dis 2021;8:3–6; 5. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 6. Salloway S, et al. Nat Med 2021;27:1187–1196. Left-hand images from J Alzheimers Dis, 28, Bohrmann B, et al. Gantenerumab: a novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β, p. 49-69, ©2012, with permission from IOS Press.

Gantenerumab clinical development program

Informed by nearly two decades of research

2000-05

Roche enters into collaboration with MorphoSys and initiates Phase I single-ascending dose study

2006

Ph I[a] (IV)

Multiple-ascending dose study in mild AD to assess effect on brain amyloid in participants with AD[1]

2008

Subcutaneous administration

Development of subcutaneous formulation

2010

Ph II

SCarlet RoAD[2]

MCI due to AD

Efficacy and safety of lower doses

Amyloid-positivity confirmation

2012

Ph II

DIAN-TU[3]

Dominant-inherited autosomal AD

Collaborative study[b]

2014

Ph III

SCarlet RoAD and Marguerite RoAD Ph III[2,4]

MCI due to AD and mild AD

SCarlet RoAD futility end 2014

2015

Ph III OLE higher dose exploration

SCarlet RoAD and Marguerite RoAD OLEs[5–7]

Amyloid removal with higher doses

Safety and tolerability of multiple titration schemes

2018

Two Ph III pivotal studies

GRADUATE I and II Ph III[8,9]

Early AD

Efficacy and safety 1,020 mg subcutaneous

- Home admin
- 27 months
- BTD in 2021

Autoinjector development

[a]Gantenerumab has been studied in single- and multiple-dose Phase I clinical trials. [b]Sponsored by Washington University School of Medicine, co-funded by Eli Lilly and Company, F. Hoffmann-La Roche Ltd, Alzheimer's Association, National Institute on Aging, GHR Foundation, anonymous organization, Avid Radiopharmaceuticals, and Accelerating Medicines Partnership. AD, Alzheimer's disease; BTD, Breakthrough Therapy Designation; DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; IV, intravenous; MCI, mild cognitive impairment; OLE, open-label extension; Ph, Phase. 1. Ostrowitzki S, et al. Arch Neurol 2012;69:198–207; 2. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 3. Salloway S, et al. Nat Med 2021;27:1187–1196; 4. Voyle N, et al. Presented at AAIC 2018, Chicago, IL, USA; 5. Klein G, et al. Presented at AAIC 2018, Chicago, IL, USA; 6. Abi-Saab D, et al. Presented at AAIC 2018, Chicago, IL, USA; 7. Andjelkovic M, et al. Presented at AAIC 2018, Chicago, IL, USA; 8. Pross N, et al. Presented at AD/PD 2019, Lisbon, Portugal; 9. F. Hoffmann-La Roche Ltd data on file.

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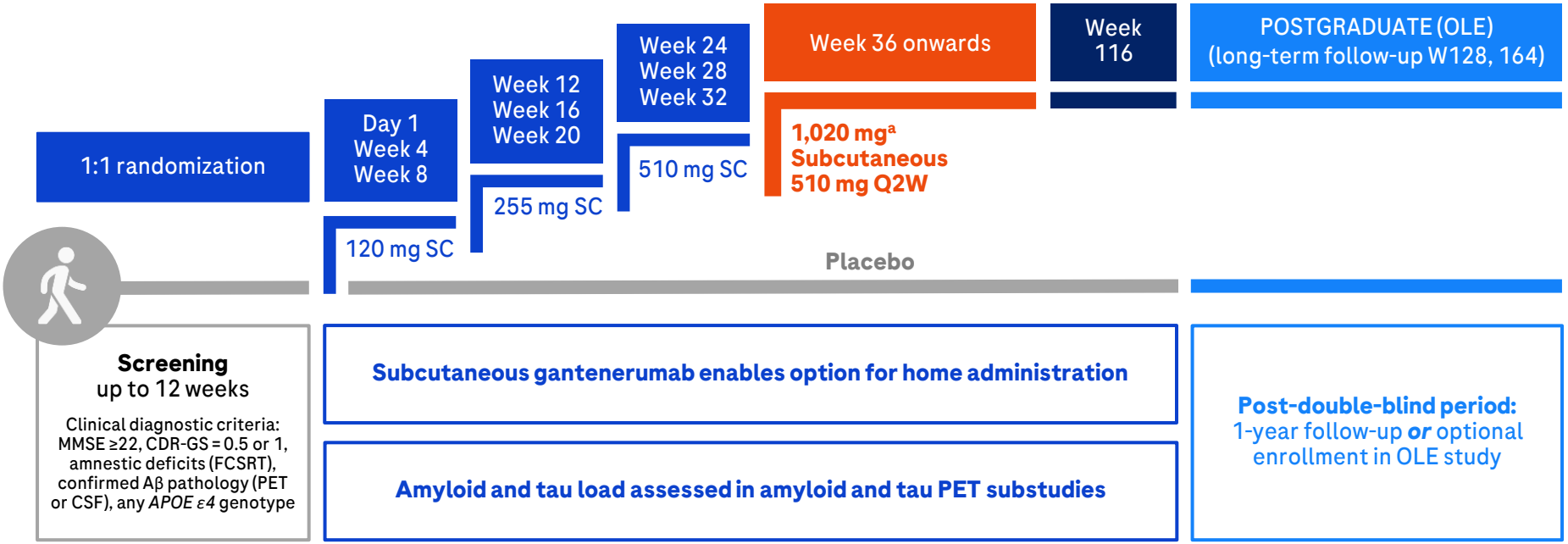
GRADUATE I and II studies assessed the efficacy and safety of subcutaneous gantenerumab in early symptomatic AD[1–5]

Two global, 27-month, randomized, identically designed, double-blind, placebo-controlled studies



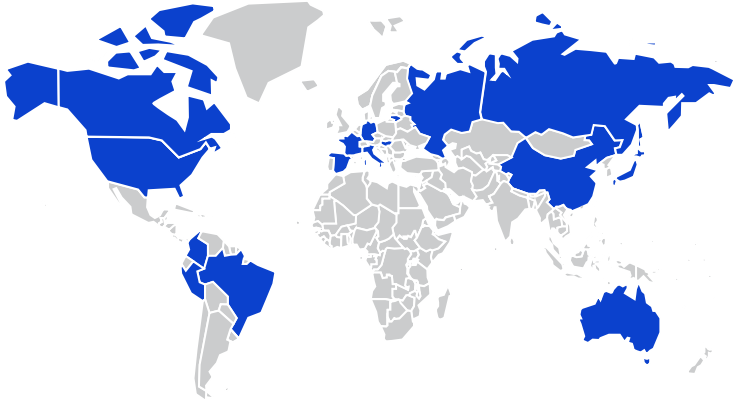
[a]1,020 mg new drug substance, based on a different manufacturing process, with similar bioavailability as 1,200 mg used in SCarlet RoAD and Marguerite RoAD OLEs.

Aβ, amyloid-beta; AD, Alzheimer's disease; *APOE ε4*, apolipoprotein E ε4 allele; CDR-GS, Clinical Dementia Rating – Global Score; CSF, cerebrospinal fluid; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; OLE, open-label extension; PET, positron emission tomography; Q2W, every 2 weeks; SC, subcutaneous. 1. ClinicalTrials.gov. ID: NCT03444870. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03444870 on November 24, 2022; 2. ClinicalTrials.gov. ID: NCT03443973. Accessed online at: https://clinicaltrials.gov/ct2/show/NCT03443973 on November 24, 2022; 3. Pross N, et al. Presented at AD/PD 2019, Lisbon, Portugal; 4. Lane C, et al. Presented at CTAD 2021, Boston, MA, USA; 5. F. Hoffmann-La Roche Ltd. data on file.

Global reach of GRADUATE I and II

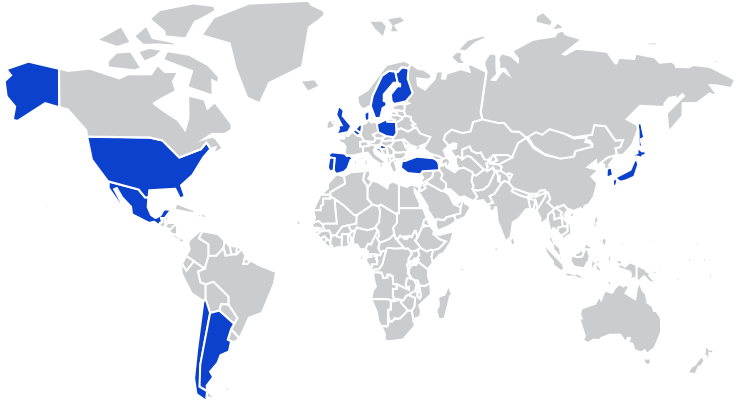
Two independent studies recruited participants in 288 sites across 30 countries, with no overlapping sites

GRADUATE I (N = 985)



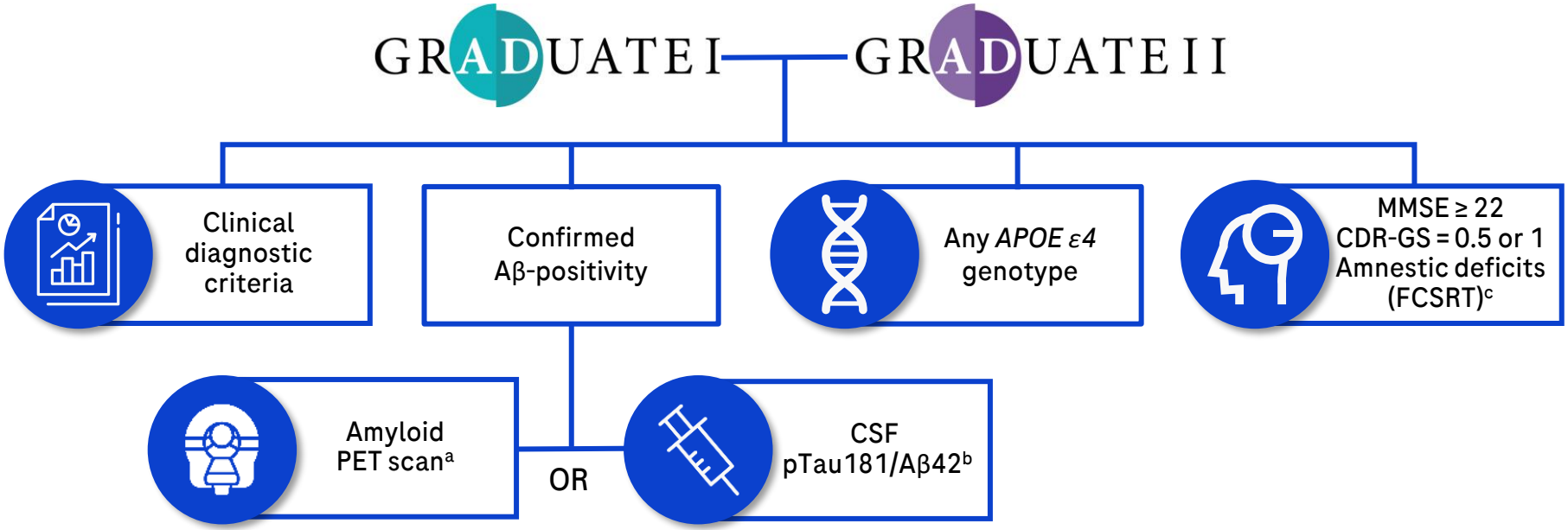
- Australia
- Brazil
- Canada
- Mainland China
- Republic of China
- Colombia
- France
- Germany
- Hungary
- Italy
- Japan
- Lithuania
- Peru
- Russian Federation
- Spain
- United States of America

GRADUATE II (N = 980)



- Argentina
- Belgium
- Chile
- Croatia
- Denmark
- Finland
- Japan
- South Korea
- Mexico
- Netherlands
- Poland
- Portugal
- Singapore
- Spain
- Sweden
- Turkey
- United Kingdom
- United States of America

Studies enrolled people living with MCI due to AD or mild AD dementia



[a]PET scan using either ^{18}F-florbetapir, ^{18}F-flutemetamol, or ^{18}F-florbetaben. Positive visual read by central PET laboratory. [b]CSF pTau to CSF Aβ42 ratio. [c]Cutoffs for FCSRT: cueing index ≤ 0.67; free recall < 27.
Aβ, amyloid-beta; AD, Alzheimer's disease; *APOE ε4*, apolipoprotein E ε4 allele; CDR-GS, Clinical Dementia Rating – Global Score; CSF, cerebrospinal fluid; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; pTau, phosphorylated tau.
Lane C, et al. Presented at CTAD 2021, Boston, MA, USA.

GRADUATE I and II include a broad range of clinically relevant measures of efficacy, safety, and biological activity

Change from baseline (Day 1) to Week 116

Efficacy endpoints	Primary endpoint	CDR-SB					
	Secondary endpoints	ADAS-Cog13	ADCS-ADL	FAQ	MMSE	Verbal fluency	Coding
	Exploratory	NPI-Q	ZCI-AD	QoL-AD	EQ-5D	RUD-Lite	
Additional endpoints	Biomarker	Amyloid PET	Tau PET	CSF[a]	Plasma	MRI	
	PK	CSF	Plasma				
	Safety	AEs	MRI	C-SSRS	Anti-drug antibodies		

[a]CSF markers include pTau181, tTau, neurogranin, neurofilament light. ADAS-Cog 13, Alzheimer's Disease Assessment Scale – Cognitive Subscale 13; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE, adverse event; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CSF, cerebrospinal fluid; C-SSRS, Columbia–Suicide Severity Rating Scale; EQ-5D, EuroQoL – Five Dimensions; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NPI-Q, Neuropsychiatric Inventory Questionnaire; PET, positron emission tomography; PK, pharmacokinetic; pTau, phosphorylated tau; QoL, Quality of Life; RUD, Resource Utilization in Dementia; tTau, total tau; ZCI-AD, Zarit Caregiver Interview – AD.

GRADUATE I and II include a broad range of clinically relevant measures of efficacy, safety, and biological activity[a]

Change from baseline (Day 1) to Week 116

Efficacy endpoints	**Primary endpoint**	**CDR-SB**					
	Secondary endpoints	**ADAS-Cog13**	**ADCS-ADL**	**FAQ**	MMSE	Verbal fluency	Coding
	Exploratory	NPI-Q	ZCI-AD	QoL-AD	EQ-5D	RUD-Lite	
Additional endpoints	**Biomarker**	**Amyloid PET**	Tau PET	**CSF[a]**	Plasma	MRI	
	PK	CSF	Plasma				
	Safety	**AEs**	**MRI**	C-SSRS	Anti-drug antibodies		

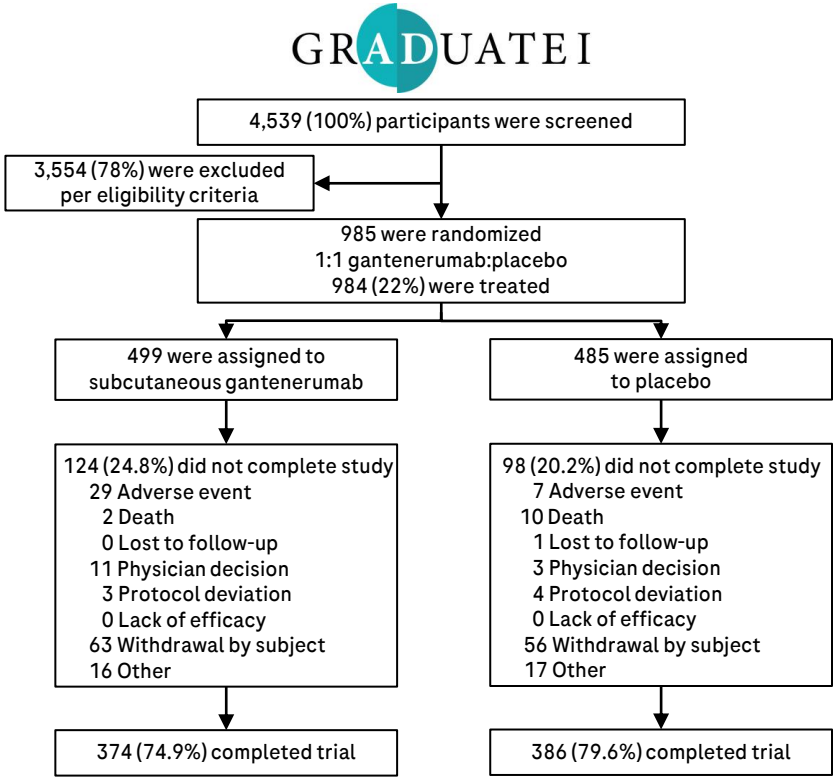
[a]This presentation will focus on the measures highlighted in blue. [b]CSF markers include pTau181, tTau, neurogranin, neurofilament light. ADAS-Cog 13, Alzheimer's Disease Assessment Scale – Cognitive Subscale 13; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE, adverse event; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CSF, cerebrospinal fluid; C-SSRS, Columbia–Suicide Severity Rating Scale; EQ-5D, EuroQoL – Five Dimensions; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NPI-Q, Neuropsychiatric Inventory Questionnaire; PET, positron emission tomography; PK, pharmacokinetic; pTau, phosphorylated tau; QoL, Quality of Life; RUD, Resource Utilization in Dementia; tTau, total tau; ZCI-AD, Zarit Caregiver Interview – AD.

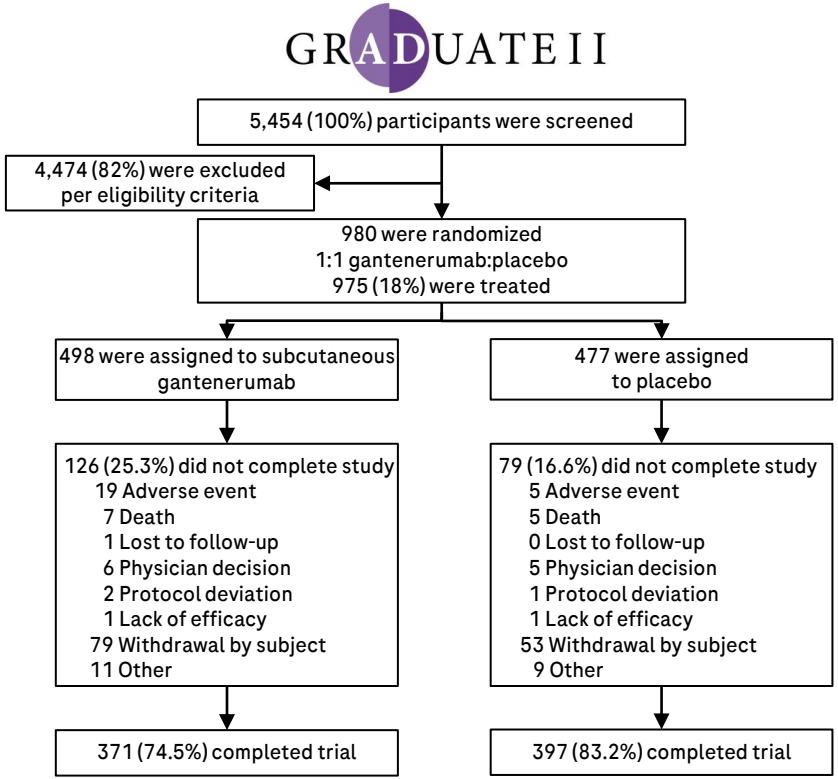
Participant disposition and baseline characteristics

Consistent population representative of early symptomatic AD across both studies

Participant disposition was similar across studies

Difference in discontinuations between placebo and gantenerumab mostly related to adverse events





Clinical cutoff date: Sep 26, 26, 2022. Information on reasons for not completing study based on disposition form for double-blind treatment period.

Baseline demographics were similar across studies

Demographics	GRADUATE I (N = 984)		GRADUATE II (N = 975)	
	Placebo (n = 485)	Gantenerumab (n = 499)	Placebo (n = 477)	Gantenerumab (n = 498)
Age, mean (SD)	72.1 (7.8)	71.1 (7.9)	71.8 (7.4)	71.6 (7.8)
Sex, female, n (%)	255 (52.6)	290 (58.1)	285 (59.7)	288 (57.8)
Race, n (%)				
American Indian or Alaska Native	18 (3.7)	18 (3.6)	13 (2.7)	13 (2.6)
Asian	53 (10.9)	52 (10.4)	75 (15.7)	56 (11.2)
Black or African American	6 (1.2)	1 (0.2)	4 (0.8)	5 (1.0)
White	398 (82.1)	414 (83.0)	385 (80.7)	424 (85.1)
Unknown	10 (2.1)	14 (2.8)	0 (0.0)	0 (0.0)
Ethnic group, n (%)				
Hispanic or Latino	58 (12.0)	52 (10.4)	119 (24.9)	112 (22.5)
Not Hispanic or Latino	422 (87.0)	439 (88.0)	358 (75.1)	386 (77.5)
Not stated / Unknown	5 (1.0)	8 (1.6)	0 (0.0)	0 (0.0)
Years of education, mean (SD)	13.6 (3.8)	13.3 (3.7)	13.3 (4.4)	13.3 (4.2)
AD symptomatic therapy at baseline, n (%)	295 (60.8)	312 (62.5)	315 (66.0)	331 (66.5)

Clinical cutoff date: Sep 26, 2022.
AD, Alzheimer's disease; SD, standard deviation.

Baseline disease characteristics related to screening criteria confirm an MCI due to AD and mild AD dementia

Disease characteristics[a] related to screening criteria	Assessment scoring range	GRADUATE I (N = 984)		GRADUATE II (N = 975)	
		Placebo (n = 485)	Gantenerumab (n = 499)	Placebo (n = 477)	Gantenerumab (n = 498)
Diagnosis at baseline, n (%) MCI due to AD Mild AD dementia	NA	 263 (54.2) 222 (45.8)	 275 (55.1) 224 (44.9)	 266 (55.8) 211 (44.2)	 269 (54.0) 229 (46.0)
CDR-GS, n (%) 0.5 1 2[a]	0–3	 359 (74.0) 123 (25.4) 3 (0.6)	 344 (68.9) 149 (29.9) 6 (1.2)	 360 (75.5) 116 (24.3) 1 (0.2)	 344 (69.2) 150 (30.2) 3 (0.6)
MMSE, mean (SD)	0–30	23.6 (3.0)	23.5 (3.3)	23.8 (3.2)	23.6 (3.1)
FCSRT, mean (SD)[b] Free recall Cueing index	 0–48 0.0–1.0[c]	 8.6 (5.6) 0.4 (0.2)	 8.9 (5.7) 0.4 (0.2)	 8.7 (5.4) 0.4 (0.2)	 9.1 (5.4) 0.4 (0.1)
Aβ assessment, n (%) CSF PET	NA	 143 (29.5) 345 (70.5)	 150 (30.1) 349 (69.9)	 117 (24.5) 360 (75.5)	 134 (26.9) 364 (73.1)
APOE ε4 allele, n (%) *0 ε4* *1 ε4* *2 ε4*	NA	 157 (32.4) 241 (49.7) 87 (17.9)	 173 (34.7) 235 (47.1) 91 (18.2)	 156 (32.7) 254 (53.2) 67 (14.0)	 165 (33.1) 242 (48.6) 91 (18.3)

Clinical cutoff date: Sep 26, 2022. [a]Baseline values; at screening all participants were confirmed to be eligible with CDR-GS of 0.5 or 1. [b]The FCSRT values presented here are values at screening; FCSRT was not assessed at baseline. [c]Data generated from Roche datasets showed that a cueing index of 0.67 is a good predictor of cognitive decline. Therefore, the FCSRT cueing index of 0.67 was selected as an inclusion criteria for this study.
Aβ, amyloid-beta; AD, Alzheimer's disease; *APOE ε4,* apolipoprotein E ε4 allele; CDR-GS, Clinical Dementia Rating – Global Score; CSF, cerebrospinal fluid; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NA; not applicable; PET, positron emission tomography; SD, standard deviation.

Baseline disease characteristics related to cognitive and functional scales confirm an MCI due to AD and mild AD dementia population

Disease characteristics related to cognitive and functional scales	Assessment scoring range	GRADUATE I (N = 984)		GRADUATE II (N = 975)	
		Placebo (n = 485)	Gantenerumab (n = 499)	Placebo (n = 477)	Gantenerumab (n = 498)
CDR-SB, mean (SD)	0–18	3.71 (1.57)	3.71 (1.67)	3.52 (1.54)	3.67 (1.61)
ADAS-Cog13, mean (SD)	0–85	28.1 (6.8)	28.1 (7.1)	28.2 (7.0)	28.1 (6.9)
ADCS-ADL total score, mean (SD)	0–78	68.2 (6.8)	67.9 (7.2)	68.9 (7.2)	68.3 (7.3)
FAQ, mean (SD)	0–30	7.8 (5.7)	8.0 (5.9)	6.8 (5.3)	7.7 (5.8)

Clinical cutoff date: Sep 26, 2022.
AD, Alzheimer's disease; ADAS-Cog 13, Alzheimer's Disease Assessment Scale – Cognitive Subscale 13; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; CDR-SB, Clinical Dementia Rating – Sum of Boxes; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; SD, standard deviation.

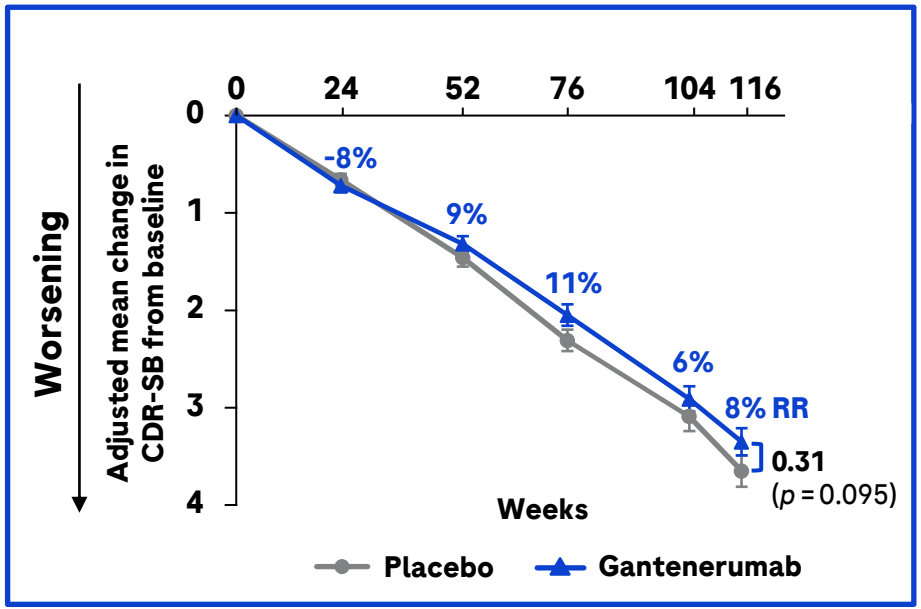
Primary endpoint: CDR-SB at Week 116

No statistically significant slowing of decline observed across the two pivotal studies

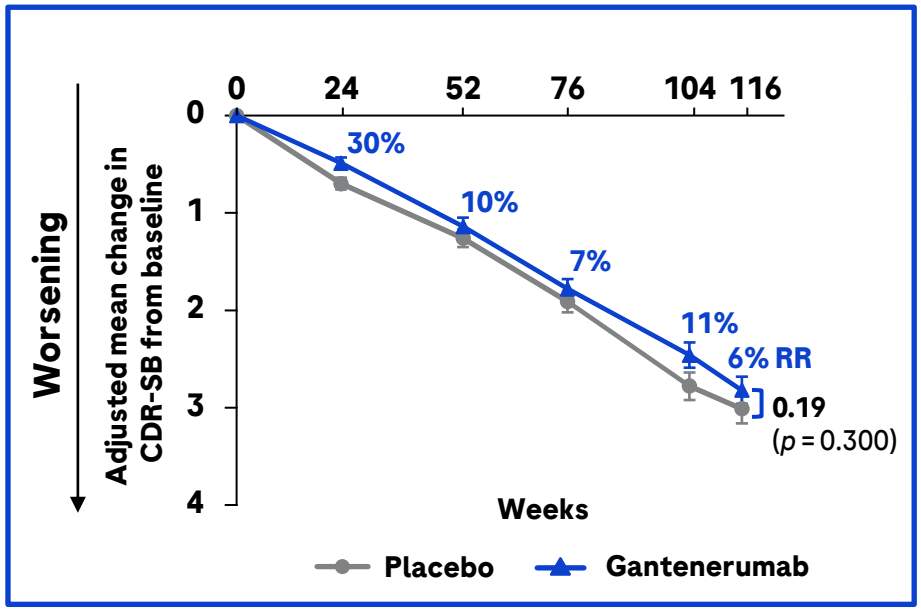
GRADUATE I and II did not meet the primary endpoint of change from baseline on CDR-SB at Week 116

Non-significant trend towards clinical effect of 6–8% relative reduction across studies

GRADUATE I



GRADUATE II

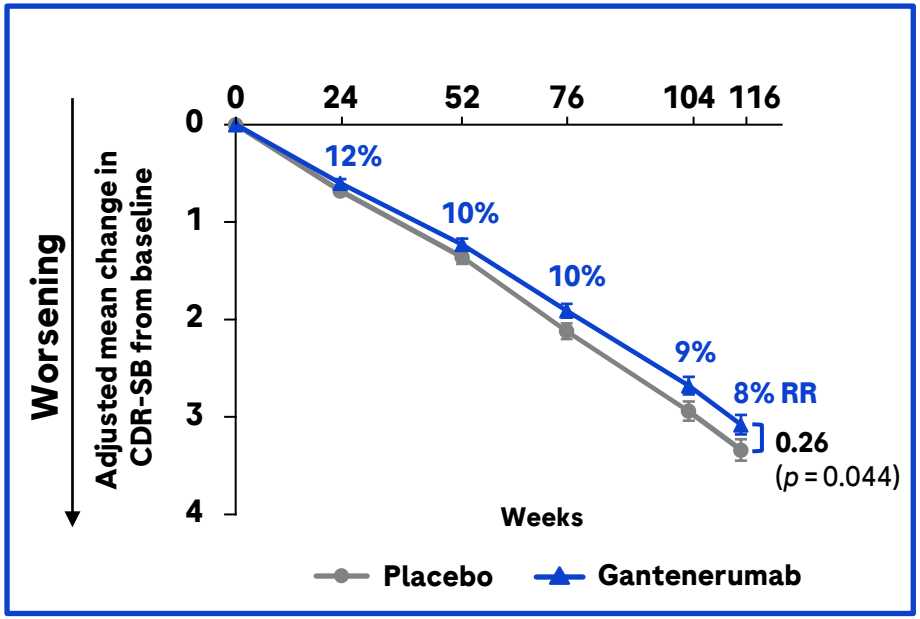


Clinical cutoff date: Sep 26, 2022.

The % values represent % RR in the gantenerumab group vs placebo. A higher CDR-SB score relates to a worsening in cognition and function. Adjusted mean plot of RBMI-ANCOVA analysis for primary endpoint CDR-SB change from baseline in the primary estimand. CDR-SB, Clinical Dementia Rating – Sum of Boxes; RBMI-ANCOVA, ANCOVA with reference-based mean imputation; RR, relative reduction.

Prespecified outcome of pooled results on CDR-SB showed a nominally significant effect in favor of gantenerumab

POOLED GRADUATE

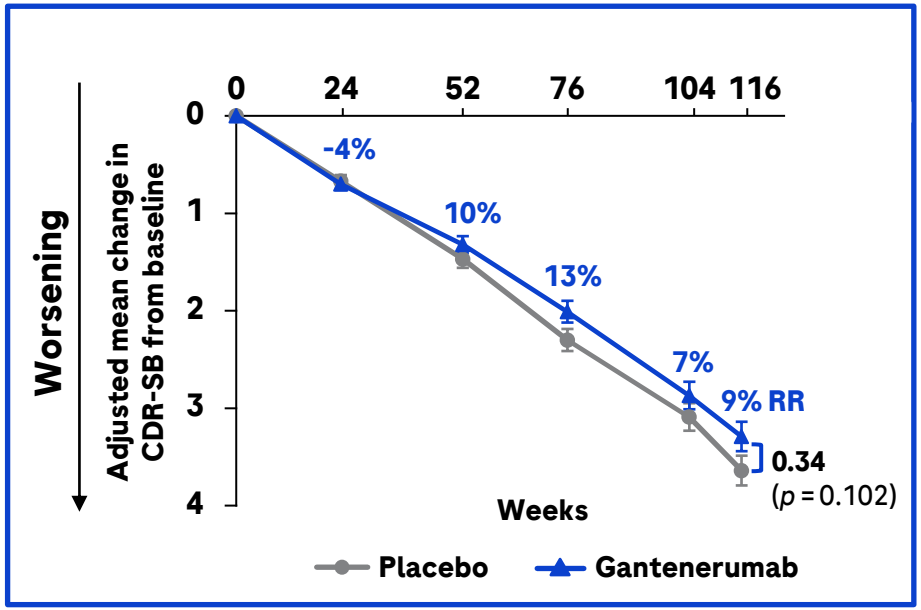


Clinical cutoff date: Sep 26, 2022.
p values are only descriptive. The % values represent % RR in the gantenerumab group vs placebo. A higher CDR-SB score relates to a worsening in cognition and function. Adjusted mean plot of RBMI-ANCOVA analysis for primary endpoint CDR-SB change from baseline in the primary estimand. CDR-SB, Clinical Dementia Rating – Sum of Boxes; RBMI-ANCOVA, ancova with reference based mean imputation; RR, relative reduction.

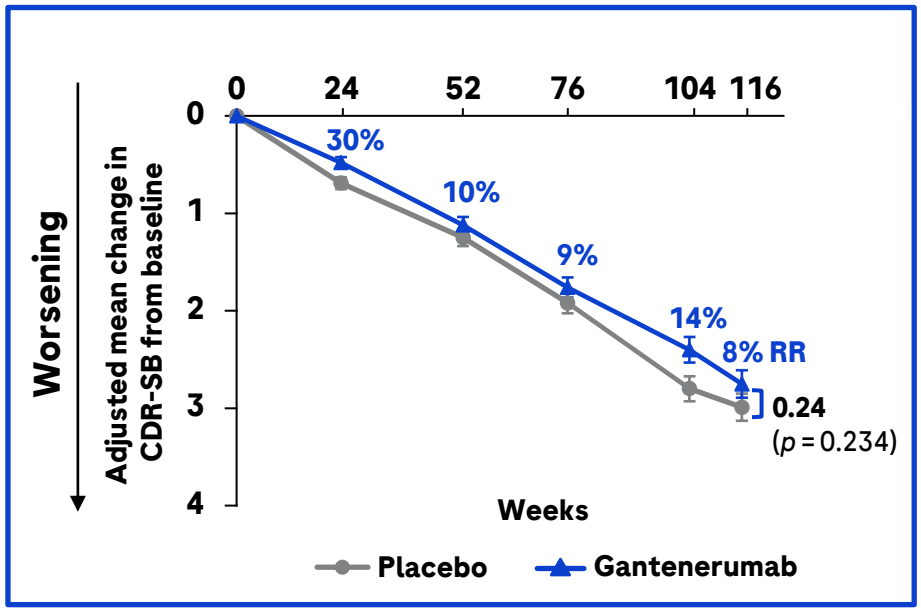
Sensitivity analysis of the primary endpoint CDR-SB with MMRM

Different statistical imputation methods do not change interpretation of results

GRADUATE I



GRADUATE II



Clinical cutoff date: Sep 26, 2022.
The % values represent % RR in the gantenerumab group vs placebo. A higher CDR-SB score relates to a worsening in cognition and function.
CDR-SB, Clinical Dementia Rating – Sum of Boxes; MMRM, mixed model for repeated measures; RR, relative reduction.

Confirmatory secondary endpoints: ADAS-Cog13, ADCS-ADL, and FAQ

No significant slowing of decline observed across the two pivotal studies

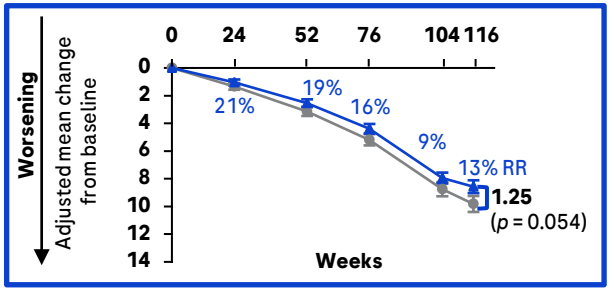
Prespecified secondary clinical outcome measures of cognition and function across both studies

Non-significant trends on ADAS-Cog13, ADCS-ADL, and FAQ ranging from 9 to 16% RR

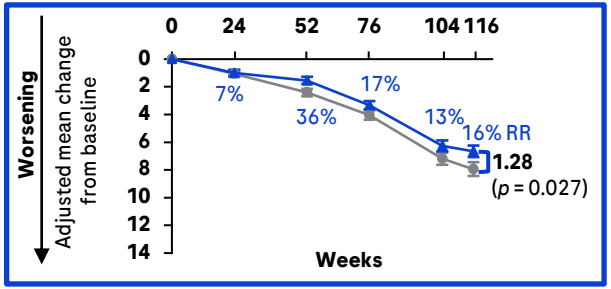
Placebo
Gantenerumab

ADAS-Cog 13

GRADUATE I

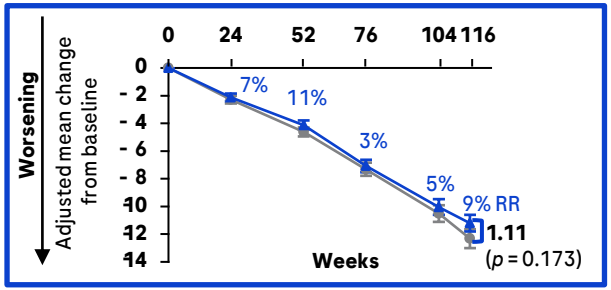


GRADUATE II

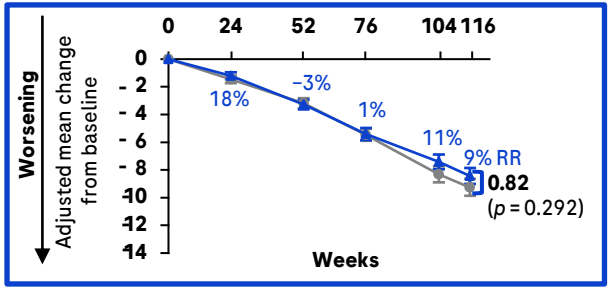


ADCS-ADL

GRADUATE I

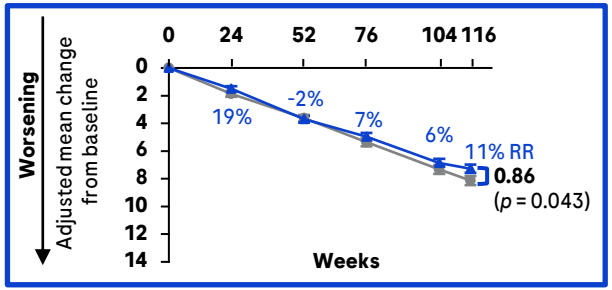


GRADUATE II

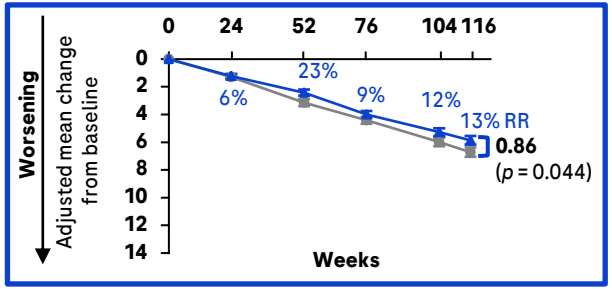


FAQ

GRADUATE I



GRADUATE II



Clinical cutoff date: Sep 26, 2022. *p* values are only descriptive. Adjusted mean plot of RBMI-ANCOVA analysis for secondary endpoints. The % values represent % RR in the gantenerumab group vs placebo. AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; FAQ, Functional Activities Questionnaire; RR, relative reduction.

Subgroup analyses on primary endpoint: Clinical stage of disease and *APOE ε4* carrier status

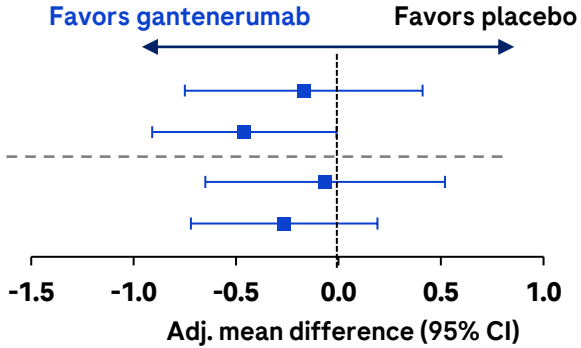
Earlier disease stage may be associated with better outcomes;
no effect of *APOE ε4* carrier status

Clinical impact on CDR-SB in two subgroups

Better treatment effect point estimate in MCI due to AD vs mild AD dementia subgroup; no effect of *APOE ε4* carrier status

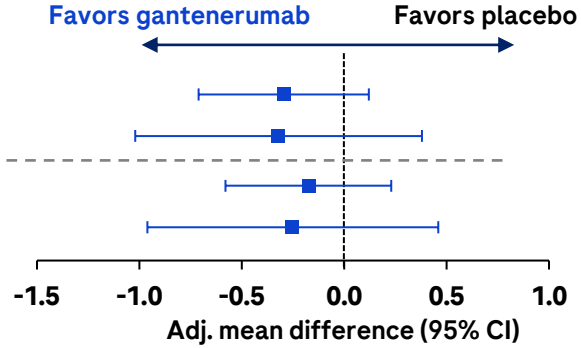
Clinical stage of disease

		n (%)	Adj. mean difference	95% CI
GRADUATE I	Mild AD dementia	446 (45.3)	−0.171	−0.75, 0.41
	MCI due to AD	538 (54.7)	−0.462	−0.91, -0.01
GRADUATE II	Mild AD dementia	440 (45.1)	−0.067	−0.65, 0.52
	MCI due to AD	535 (54.9)	−0.266	−0.72, 0.19



APOE ε4 carrier status

		n (%)	Adj. mean difference	95% CI
GRADUATE I	*ε4* carrier	654 (66.5)	−0.294	−0.71, 0.12
	ε4 non carrier	330 (33.5)	−0.321	−1.02, 0.38
GRADUATE II	*ε4* carrier	654 (67.1)	−0.172	−0.58, 0.23
	ε4 non carrier	321 (32.9)	−0.253	−0.96, 0.46



RBMI-ANCOVA analysis for primary endpoint: CDR-SB change from baseline in the primary estimand.

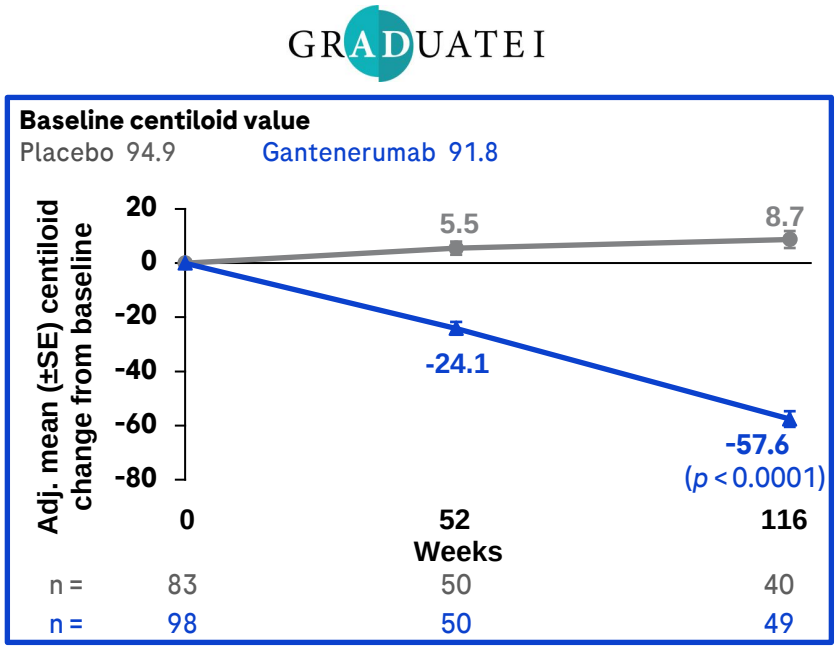
AD, Alzheimer's disease; Adj, adjusted; *APOE ε4*, apolipoprotein E ε4 allele; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CI, confidence interval; MCI, mild cognitive impairment.

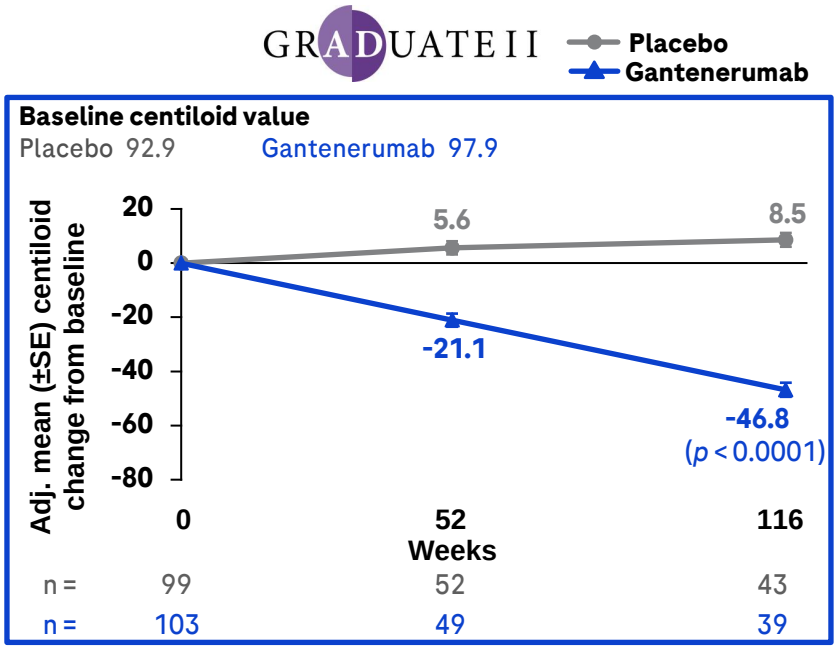
Biomarkers:
Amyloid PET substudies

Confirmed evidence of target engagement, at a magnitude lower than expected

Gantenerumab reduced amyloid plaque at Weeks 52 and 116, but below expectations

Significant pharmacodynamic effect on amyloid PET reduction in the GRADUATE I and II PET substudies



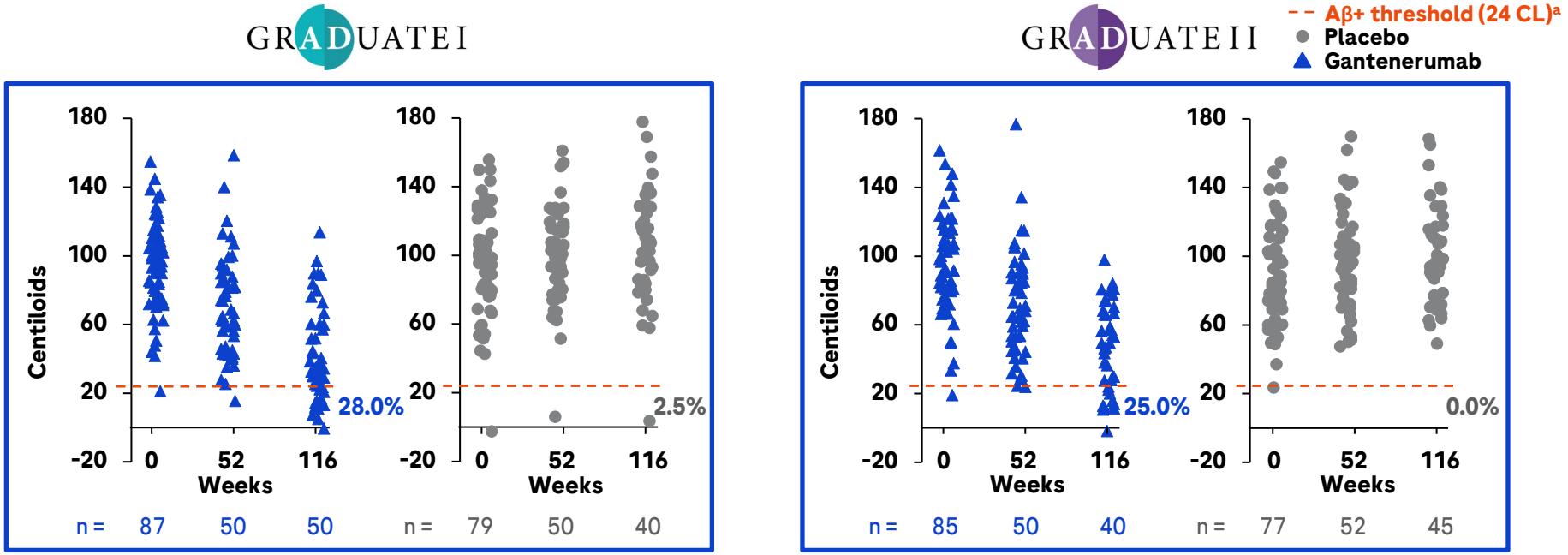


Centiloid reduction in relevant population was 42 CL at Week 52 and 71 CL at Week 104[1,a]

The values in blue represent the adjusted mean centiloid change from baseline for gantenerumab group. The values in grey represent the adjusted mean centiloid change from baseline for placebo group. Estimates and *p* values from MMRM. [a]Based on data from Marguerite RoAD OLE non-pretreated population. CL, centiloid; MMRM, mixed model for repeated measures; OLE, open-label extension; PET, positron emission tomography; SE, standard error. 1. Klein G, et al. Alz Res Ther 2019;11:101.

Gantenerumab reduced amyloid plaque levels below amyloid-positivity threshold in fewer participants than expected

Proportion of participants reaching amyloid-negativity half of anticipated



% of participants below positivity threshold in relevant population was 26% at Week 52 and 50% at Week 104[1,b]

Clinical cutoff date: Sep 26, 2022. [a]24 CL is the amyloid-positivity threshold. [b]Based on data from Marguerite RoAD OLE non-pretreated population. Aβ, amyloid-beta; CL, centiloid; OLE, open-label extension. 1. Klein G, et al. Alz Res Ther 2019;11:101.

Exploratory *post-hoc* analysis in participants above and below threshold in the amyloid PET substudies

Greater amyloid plaque removal may result in a larger magnitude of effect on CDR-SB

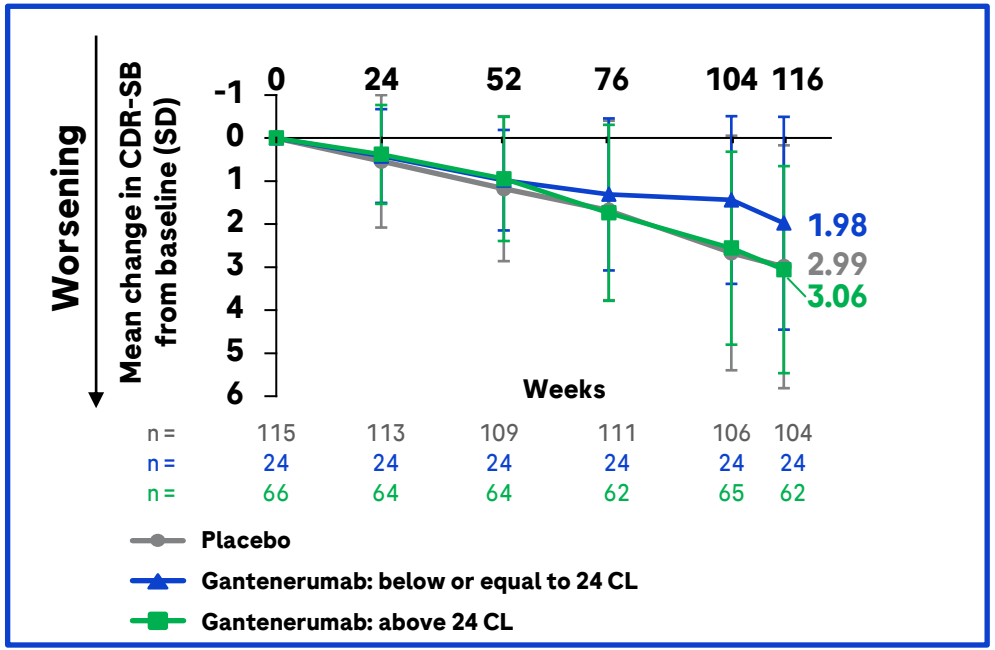
Exploratory *post-hoc* comparison in participants above vs below amyloid-positivity threshold

Hypothesis: Amount of amyloid PET removal may relate to clinical outcomes

POOLED GRADUATE

Preliminary data; further evaluations ongoing

- Limitations
  - Potential confounding factors may account for these observations, including baseline characteristic imbalances such as:
    - Older age
    - Lower body weight
    - Earlier in disease course
  - Very small sample size



Data shown are descriptive summary statistics. The values at the end of the graph are the mean change from baseline at Week 116. A higher CDR-SB score relates to a worsening in cognition and function. CDR-SB, Clinical Dementia Rating – Sum of Boxes; CL, centiloid; PET, positron emission tomography; SD, standard deviation.

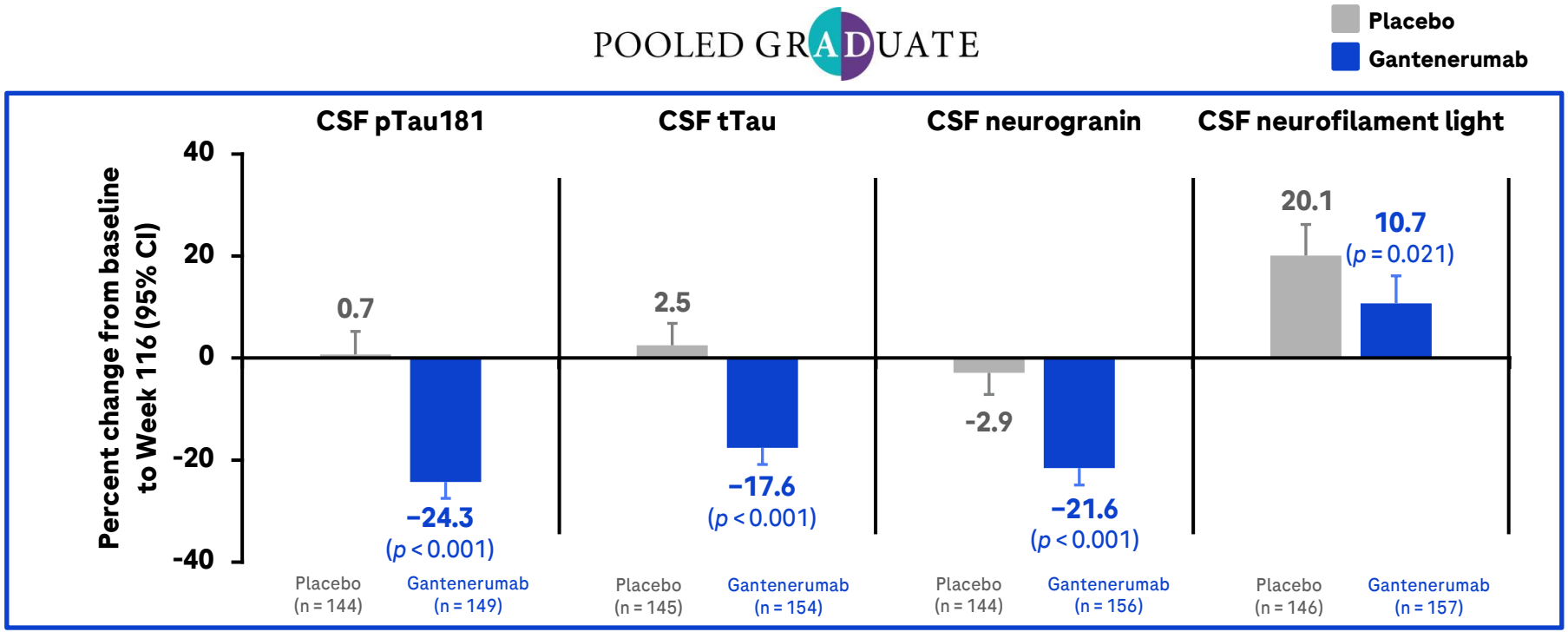
Biomarkers: CSF

Evidence of downstream effect on biomarkers of AD pathology and neurodegeneration

Preliminary prespecified pooled analysis showed effect of gantenerumab on downstream CSF biomarkers

Evidence of pharmacodynamic effect on CSF biomarkers[a]

POOLED GRADUATE



Clinical cutoff date: Sep 26, 2022. *p* values are descriptive only. [a]Small number of samples awaiting processing. Adjusted mean plot of ANCOVA analysis for CSF biomarker % change from baseline to Week 116.
CI, confidence interval; CSF, cerebrospinal fluid; MMRM, mixed model repeated measures; pTau, phosphorylated tau; tTau, total tau.

Safety

Subcutaneous gantenerumab was well tolerated in the GRADUATE I and II studies

Subcutaneous gantenerumab was well tolerated across the GRADUATE I and II studies

	GRADUATE I (N = 984)		GRADUATE II (N = 975)	
	Placebo (n = 481)	Gantenerumab (n = 503)	Placebo (n = 474)	Gantenerumab (n = 501)
Participants with an AE, n (%)	423 (87.9)	454 (90.3)	409 (86.3)	451 (90.0)
Participants with an SAE, n (%)	95 (19.8)	76 (15.1)	63 (13.3)	61 (12.2)
Participants permanently discontinuing treatment due to AEs, n (%)[a]	10 (2.1)	47 (9.3)	7 (1.5)	44 (8.8)
Participants with AE with fatal outcome, n (%)[b]	10 (2.1)	3 (0.6)	4 (0.8)	7 (1.4)

Clinical cutoff date: Sep 26, 2022. Safety-evaluable population (patients received at least one dose of study drug).
[a]Most frequently reported AEs by MedDRA preferred terms (> 1 participant across both studies) leading to discontinuation include ARIA-H, cerebral hemorrhage, ARIA-E, asthenia, cerebral infarction, confusional state, delirium, and subdural hematoma. [b]All AEs with fatal outcome were considered unrelated to study treatment by PI and sponsor; included fatal outcomes in double-blind treatment period and safety follow-up period.
AE, adverse event; ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid-related imaging abnormalities – hemosiderosis; MedDRA, Medical Dictionary for Regulatory Activities; PI, Principal Investigator; SAE, serious adverse event.

Most common adverse events were consistent across studies

Most frequently reported AEs in either treatment group[a]	GRADUATE I (N = 984)		GRADUATE II (N = 975)	
	Placebo (n = 481)	Gantenerumab (n = 503)	Placebo (n = 474)	Gantenerumab (n = 501)
Injection-site reaction, n (%)[b]	43 (8.9)	94 (18.7)	31 (6.5)	75 (15.0)
Amyloid-related imaging abnormality – edema/effusion (ARIA-E), n (%)[c]	5 (1.0)	105 (20.9)	12 (2.5)	114 (22.8)
Fall, n (%)	62 (12.9)	63 (12.5)	52 (11.0)	50 (10.0)
Headache, n (%)	43 (8.9)	60 (11.9)	50 (10.5)	64 (12.8)
Nasopharyngitis, n (%)	33 (6.9)	46 (9.1)	49 (10.3)	45 (9.0)
Dizziness, n (%)	41 (8.5)	45 (8.9)	29 (6.1)	39 (7.8)
Arthralgia, n (%)	30 (6.2)	37 (7.4)	44 (9.3)	39 (7.8)
COVID-19, n (%)	44 (9.1)	29 (5.8)	33 (7.0)	39 (7.8)

Clinical cutoff date: Sep 26, 2022. Safety-evaluable population (patients received at least one dose of study drug). Percentages are based on N in the column headings. Only treatment-emergent AEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. The order is based on pooled frequencies across the two studies. [a]By preferred term (safety-evaluable population). [b]All ISRs were non-serious and mild or moderate, and without impact on treatment continuation. [c]According to the protocol, ARIA-E had to be reported as an AE if it was symptomatic, led to dosing intervention, or was otherwise considered clinically significant by the PI. AE, adverse event; ARIA-E, amyloid-related imaging abnormalities – edema; ISR, injection-site rection; PI, Principal Investigator.

ARIA-E was manageable and mostly asymptomatic

Symptomatic ARIA-E in 5%[a] and serious symptomatic ARIA-E in 1%[a] of treated participants

	GRADUATE I (N = 973)		GRADUATE II (N = 966)	
	Placebo (N = 476)	Gantenerumab (N = 497)	Placebo (N = 470)	Gantenerumab (N = 496)
Incidence of ARIA-E, n/N (%)	8/476 (1.7)	119/497 (23.9)	18/470 (3.8)	128/496 (25.8)
ARIA-E by *APOE ε4* genotype, n/N (%)				
0 ε4	2/155 (1.3)	20/172 (11.6)	7/155 (4.5)	24/163 (14.7)
1 ε4	4/237 (1.7)	57/236 (24.2)	6/249 (2.4)	60/242 (24.8)
2 ε4	2/84 (2.4)	42/89 (47.2)	5/66 (7.6)	44/91 (48.4)
Recurrent ARIA-E, n/N (%)	0/476 (0)	48/497 (9.7)	3/470 (0.6)	47/496 (9.5)
Symptomatic ARIA-E, n/N (%)[b]	0/476 (0)	26/497 (5.2)	2/470 (0.4)	24/496 (4.8)
Serious symptomatic ARIA-E, n/N (%)[c]	0/476 (0)	7/497 (1.4)	0/470 (0)	4/496 (0.8)
Radiologic severity (BGTS):				
Mean (SD)	2.8 (2.5)	9.4 (7.6)	4.0 (3.2)	8.5 (7.6)
≥ 4, n (%)[d]	2 (25.0)	155 (81.2)	9 (42.9)	138 (73.0)

Clinical cutoff date: Sep 26, 2022. MRI safety-evaluable population (patients received at least one dose of study drug and had at least one post-baseline MRI).
[a]Incidence of ARIA-E across the pooled gantenerumab arms. [b]Symptomatic ARIA-E is defined as ARIA-E temporally associated with CNS symptoms. [c]Either the ARIA-E or CNS symptom(s) were reported as a serious AE. [d]BGTS score ≥ 4 is considered radiologically moderate or severe. The majority of CNS symptoms associated with ARIA-E resolved. CNS symptoms associated with ARIA-E that were reported as a serious adverse event included encephalopathy, aphasia, confusional state, focal dyscognitive seizures, hemianopia, mental status changes, myoclonus, psychomotor retardation, and vestibular disorder. All the serious CNS symptoms resolved; however, two with sequelae. AE, adverse event; *APOE ε4*, apolipoprotein E ε4 allele; ARIA-E, amyloid-related imaging abnormalities – edema; BGTS, Barkhof Grand Total Scale; CNS, central nervous system; SD, standard deviation.

Incidence of ARIA-H is comparable between studies and balanced between treatment arms for isolated ARIA-H

	GRADUATE I (N = 973)		GRADUATE II (N = 966)	
	Placebo (n = 476)	Gantenerumab (n = 497)	Placebo (n = 470)	Gantenerumab (n = 496)
Overall incidence of ARIA-H, n (%)	59 (12.4)	118 (23.7)	57 (12.2)	109 (22.0)
Incidence of isolated ARIA-H, n (%)[a]	55 (11.6)	46 (9.3)	53 (11.3)	39 (7.9)
At least one ARIA-H and at least one ARIA-E, n (%)[b]	4 (0.8)	72 (14.5)	4 (0.9)	70 (14.1)

Clinical cutoff date: Sep 26, 2022. MRI safety-evaluable population (patients received at least one dose of study drug and had at least one post-baseline MRI).
[a]Participants who did not develop incident ARIA-E during the study period. [b]ARIA-E and ARIA-H MRI findings do not need to temporally co-occur to qualify a participant for this category.
ARIA-E, amyloid-related imaging abnormalities – edema; ARIA-H, amyloid related imaging abnormalities– hemosiderosis; MRI, magnetic resonance imaging.

Summary

- GRADUATE I and II were designed to deliver robust results on the benefit–risk profile of gantenerumab in early symptomatic AD
- Studies did not meet their primary endpoint, with a non-significant trend towards clinical effect of gantenerumab on CDR-SB at Week 116
  - Results were consistent across studies and across secondary endpoints
  - Level of amyloid plaque reduction was significant, but lower than expected
  - Gantenerumab showed an effect on downstream CSF biomarkers
- Gantenerumab was well tolerated with the most common AEs being ARIA-E and injection-site reactions
  - ARIA-E was manageable and mostly asymptomatic
  - Injection-site reactions did not impact treatment continuation
- Additional data, including exposure, biomarker, and subgroup analyses will be shared with the AD community

AD, Alzheimer's disease; AE, adverse event; ARIA-E, amyloid-related imaging abnormalities – edema; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CSF, cerebrospinal fluid; ISR, injection-site reaction.

Implications for gantenerumab's development program

- All gantenerumab studies in early symptomatic AD are being discontinued, including GRADUATION, Open RoAD, and POSTGRADUATE
- The SKYLINE study in secondary AD prevention is also being discontinued
- Investigators have been informed and are reaching out to study participants and their families
- Discussions are ongoing with DIAN-TU regarding next steps for DIAN-001 OLE and the DIAN-002 primary prevention study with gantenerumab in autosomal-dominant AD
- Roche continues to be committed to developing and delivering diagnostic tests and therapeutic treatments in Alzheimer's disease

AD, Alzheimer's disease; DIAN-TU, Dominantly Inherited Alzheimer's Network Trials Unit; OLE, open-label extension.

Acknowledgments

We thank all **the study participants and their families, the investigators and site staff, and the entire study team** for their time and commitment to the GRADUATE studies

Steering committee members

Jeff Cummings
Randall Bateman
Kaj Blennow
Mercè Boada
Michael Donohue
Nick Fox
Takeshi Iwatsubo
Stephen Salloway
Philip Scheltens
Reisa Sperling
Bruno Vellas

Cross-functional study team

Danielle Abi-Saab
Mirjana Andjelkovic
Sophie Banzet
Szofia Bullain
Uli Burger
Patricia Ehrhard
Mar Ferreró
Neil Finch
Garry Francis
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Chris Pelentrides
Nathalie Pross
Smiljana Ristic
Loes Rutten-Jacobs
Andres Schneider
Dietmar Schwab
Alison Searle
Matteo Tonietto
Nicola Voyle
Susan Yule

Members of the Independent Data Monitoring Committee (IDMC)

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