Brainshuttle™ AD

Interim biomarker results for trontinemab, a novel Brainshuttle™ antibody in development for the treatment of Alzheimer's disease

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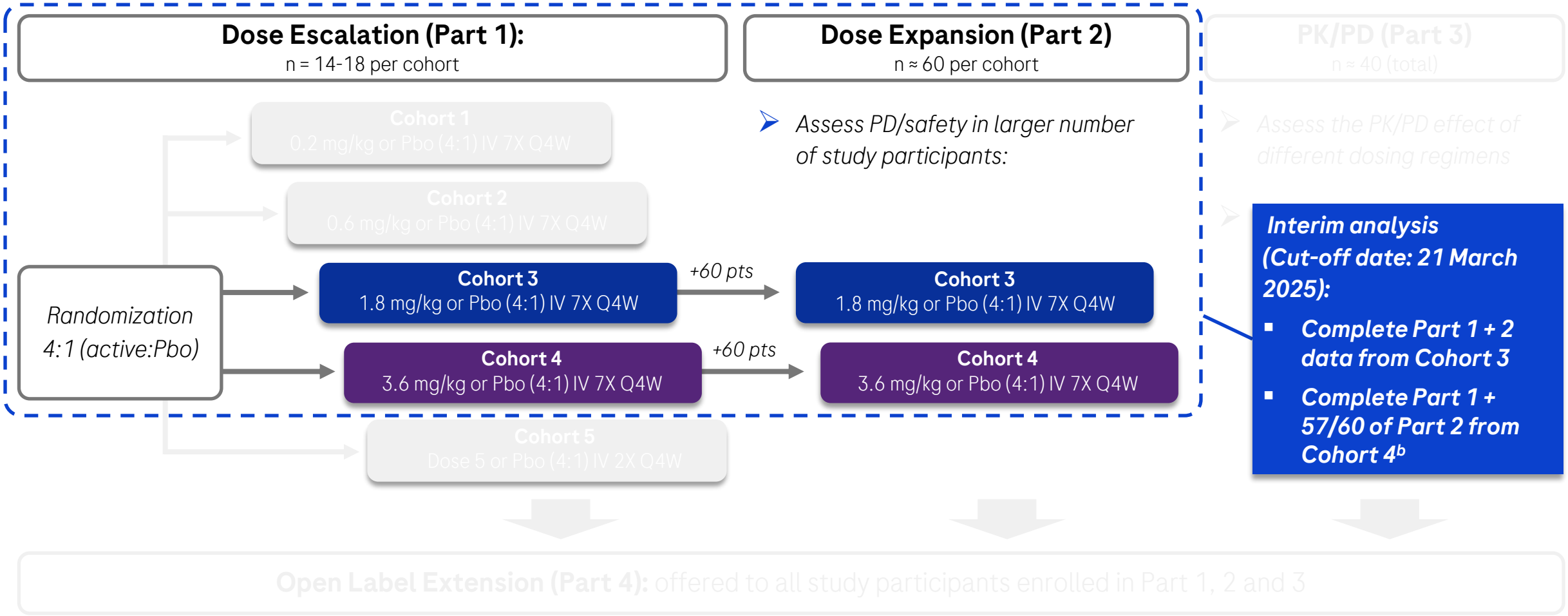
Disclosures

- **Gregory Klein** is a full-time employee and owns stocks in F. Hoffmann-La Roche Ltd
- Matteo Tonietto, Daria Rukina, Fabien Alcaraz, Carsten Hofmann, Maddalena Marchesi, Jakub Wojtowicz, João A. Abrantes, Franziska Schaedeli Stark, Paul Delmar, Hanno Svoboda, Iris Wiesel and Luka Kulic are full-time employees of and own stocks in F. Hoffmann-La Roche Ltd
- Gil Rabinovici has provided consultation to Eli Lilly, Johnson & Johnson, Merck, Novo Nordisk and Roche. He receives research support as PI/MPI from NIH/NIA P30-AG062422, R35-AG072362, U01-AG057195, U01-AG082350, R56-AG075744; NIH/NINDS R01-NS139383; Alzheimer's Association, American College of Radiology, Genentech, and Rainwater Charitable Foundation. He is an associate editor for JAMA and JAMA Neurology
- Henrik Zetterberg has served at scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD; is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program; and is a shareholder of MicThera (outside submitted work)
- Tobias Bittner is a full-time employee of F. Hoffmann-La Roche Ltd and Genentech, Inc., a member of the Roche Group, and owns stocks in F. Hoffmann-La Roche Ltd
- Ruth Croney and David Agnew are employees of Roche Products Ltd, and own stock or stock options in F. Hoffmann-La Roche Ltd
- Silke Ahlers is an external business partner of F. Hoffmann-La Roche Ltd

Brainshuttle™ AD study design

Phase Ib/IIa study assessing the safety, tolerability, PK and PD of trontinemab in participants with AD[a]



Trontinemab is an investigational product not approved for use in any market.

[a]Study population: participants diagnosed with MCI due to AD or mild-to-moderate AD, consistent with the NIA-AA diagnostic criteria[1,2]; amyloid PET: > 50 CL; MMSE: 18–28; CDR-GS: 0.5-2. [b]Three of 60 participants in Cohort 4 of Part 2 did not have the opportunity to complete the double-blind treatment period as of the 21 March 2025 cut-off date. AD, Alzheimer's disease; CDR-GS, Clinical Dementia Rating-Global Score; CL, Centiloid; IV, intravenous; Pbo, placebo; PD, pharmacodynamics; PK, pharmacokinetics; pts, participants; PET, positron emission tomography; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NIA-AA, National Institute on Aging-Alzheimer's Association; Q4W, every four weeks.

1. Albert MS, et al. Alzheimers Dement 2011;7:270–9; 2. McKhann GM, et al. Alzheimers Dement 2011;7:263–9.

Biomarkers in Part 1 (dose escalation) + Part 2 (dose expansion)

Schedule of assessments

Visit (# doses)	Screening/BL (0)	D22 (Dose 1)	D50 (Dose 2)	D78 (Dose 3)	D106 (Dose 4)	D134 (Dose 6)	D162 (Dose 6)	D172/176[a] (Dose 7)	D183 (Dose 7)	D196 (Dose 7)
Part 1 (dose escalation)	Aβ PET			Aβ PET						Aβ PET
	vMRI	vMRI		vMRI			vMRI			
	CSF							CSF		
	Plasma			Plasma					Plasma	

Trontinemab is an investigational product not approved for use in any market.
Schedule of assessments are shown for Cohorts 1-4. [a]Part 2 CSF at D174 (Day 6 post Dose 7).
Aβ, amyloid beta; BL, baseline; CSF, cerebrospinal fluid; D, day; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

Biomarkers in Part 1 (dose escalation) + Part 2 (dose expansion)

Schedule of assessments

Visit (# doses)	Screening/BL (0)	D22 (Dose 1)	D50 (Dose 2)	D78 (Dose 3)	D106 (Dose 4)	D134 (Dose 6)	D162 (Dose 6)	D172/176[a] (Dose 7)	D183 (Dose 7)	D196 (Dose 7)
Part 1 (dose escalation)	Aβ PET			Aβ PET						Aβ PET
	vMRI	vMRI		vMRI			vMRI			
	CSF							CSF		
	Plasma			Plasma					Plasma	
Part 2 (dose expansion)	Aβ PET		Aβ PET[b]	Aβ PET[b]	Aβ PET[b]					Aβ PET
	vMRI	vMRI		vMRI			vMRI			
	CSF							CSF[a]		
	Plasma	Plasma		Plasma		Plasma			Plasma	

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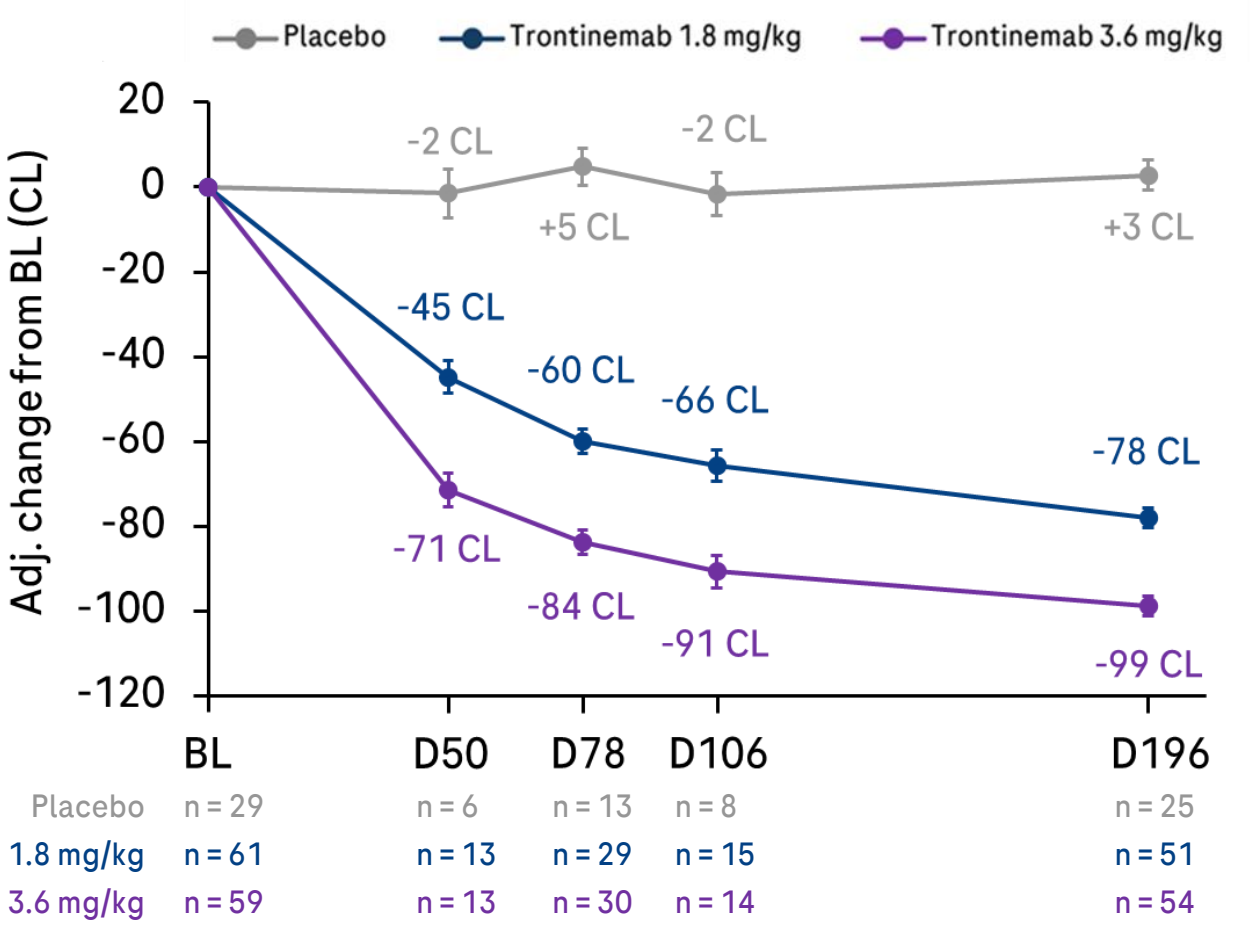
Schedule of assessments are shown for cohorts 1-4. [a]Part 2 CSF at D174 (Day 6 post dose 7). [b]Part 2 Aβ PET randomized to D50, D78 or D106. PET scan acquired Day 22 post dose for D22, D50, D78, D106, and Day 28 post Dose 7 for D196. MRI acquired Day 22 post dose for all visits. Plasma sample taken Day 22 post dose for all samples. Aβ, amyloid beta; BL, baseline; CSF, cerebrospinal fluid; D, day; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

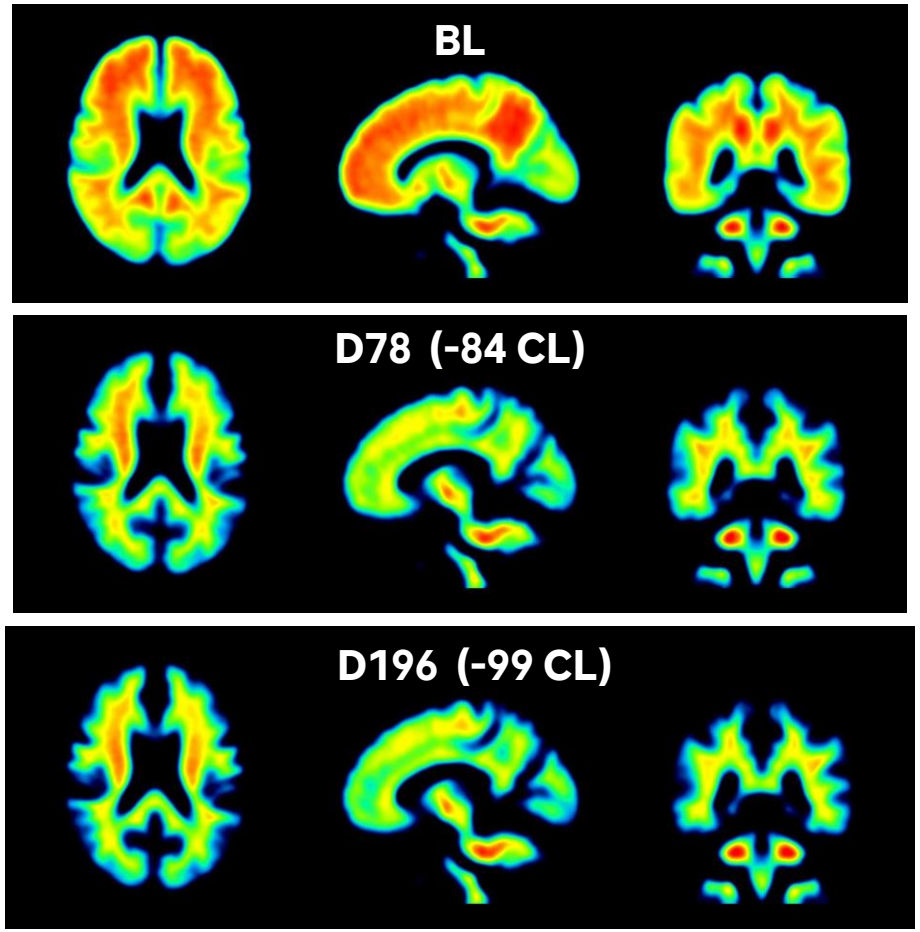
Amyloid PET

Adjusted mean change from BL after 28 weeks (Part 1 + 2 combined)[a]

Rapid and robust amyloid PET reduction at trontinemab 1.8 mg/kg and 3.6 mg/kg



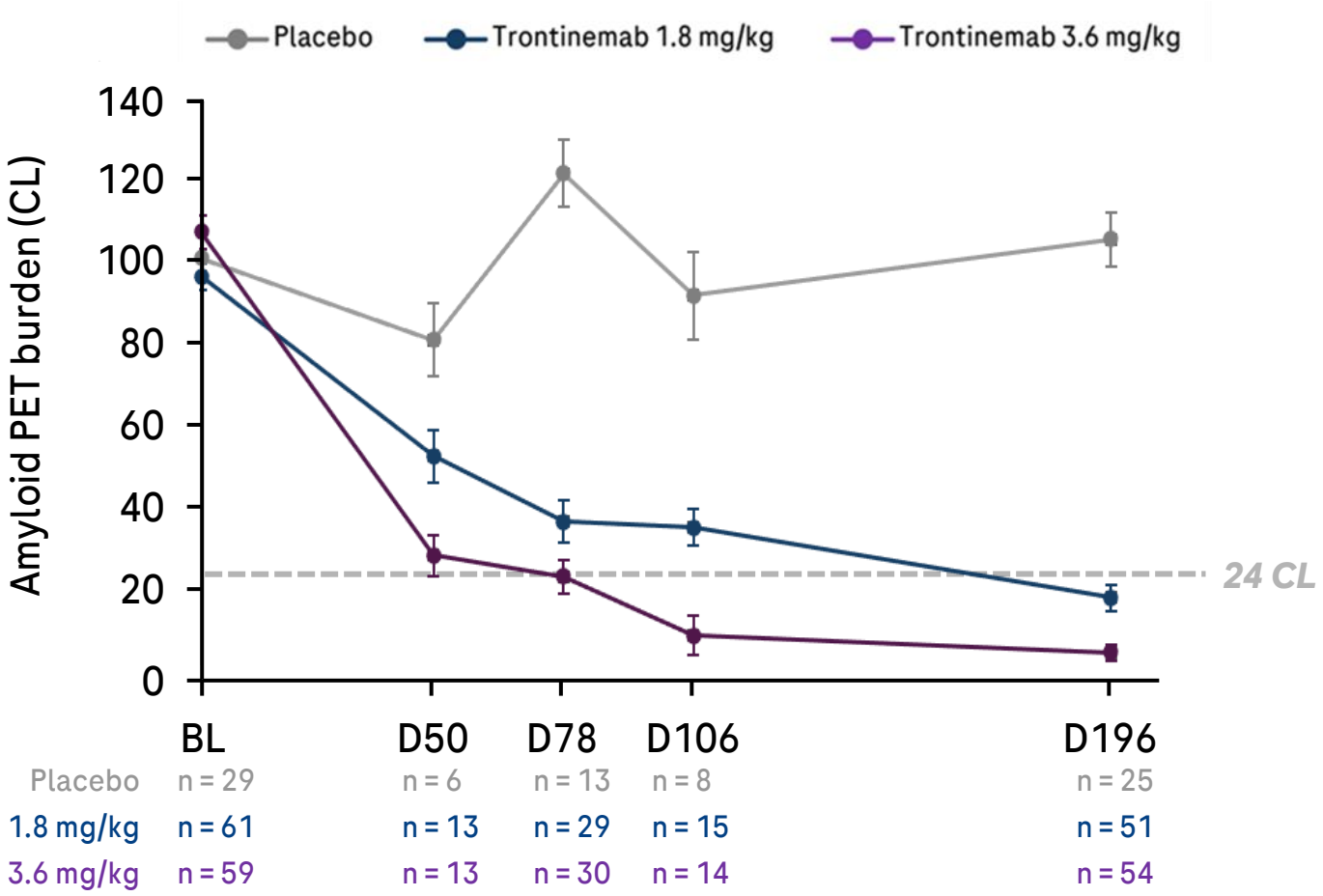
Average images of participants receiving 3.6 mg/kg[b]



Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. [a]Values at each time point were based on an MMRM model, with change from baseline in amyloid PET burden (CL) as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction and baseline amyloid PET. 'n' represents the number of participants contributing to the model with available change from baseline at each visit. [b]Global CL transformation used to compute voxelwise average in MNI space. Adj, adjusted; BL, baseline; CL, Centiloid; D, day; MMRM, mixed models for repeated measures; MNI, Montreal Neurological Institute; PET, positron emission tomography.

Absolute amyloid PET burden after 28 weeks (Part 1 + 2 combined)

91% of participants were below the amyloid positivity threshold[a]



	Mean amyloid value in CL at visit Participants ≤ 24 CL (%)[a]		
Visit	**Pbo**	**1.8 mg/kg**	**3.6 mg/kg**
BL	101 CL 0/29 (0%)	97 CL 0/61 (0%)	108 CL 0/59 (0%)
D50	81 CL 0/6 (0%)	53 CL 1/13 (8%)	29 CL 5/13 (39%)
D78	122 CL 0/13 (0%)	37 CL 12/29 (41%)	24 CL 19/30 (63%)
D106	92 CL 0/8 (0%)	36 CL 4/15 (27%)	9 CL 10/14 (71%)
D196	106 CL 0/25 (0%)	**19 CL** 33/51 **(65%)**	**5 CL** 49/54 **(91%)**

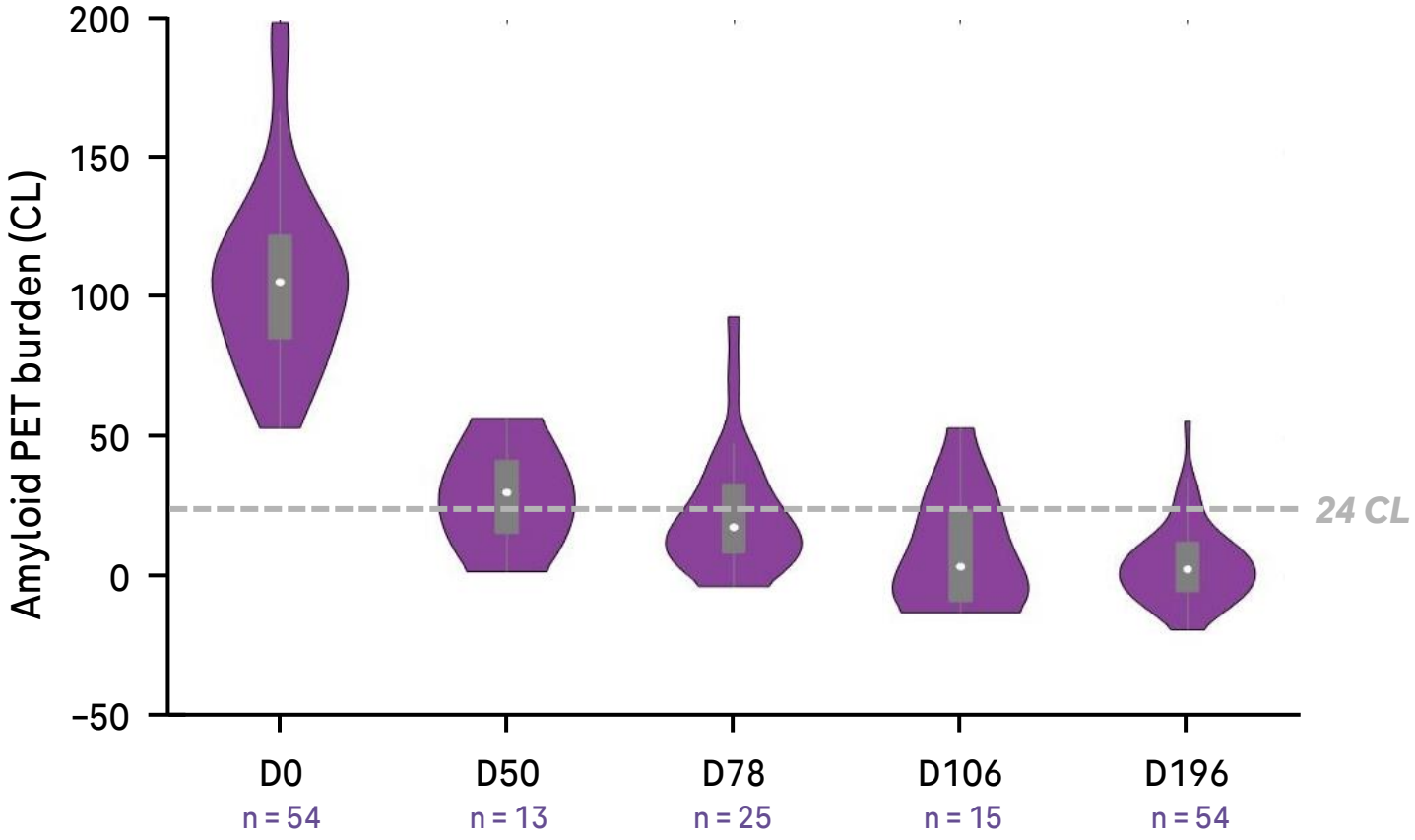
	Participants ≤ 11 CL (%)		
Visit	**Pbo**	**1.8 mg/kg**	**3.6 mg/kg**
D196	0/25 (0%)	24/51 **(47%)**	39/54 **(72%)**

Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. Mean values ±SE of available PET results at the different visit time points are plotted. [a]Amyloid positivity threshold defined as values ≤ 24 CL. Participants were randomized across intermediate timepoints (D50, D78, D106) leading to variability in placebo arm. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with Centiloid). BL, baseline; CL, Centiloid; D, day; PET, positron emission tomography; SE, standard error.

Deep amyloid depletion after 28 weeks (Part 1 + 2 combined)

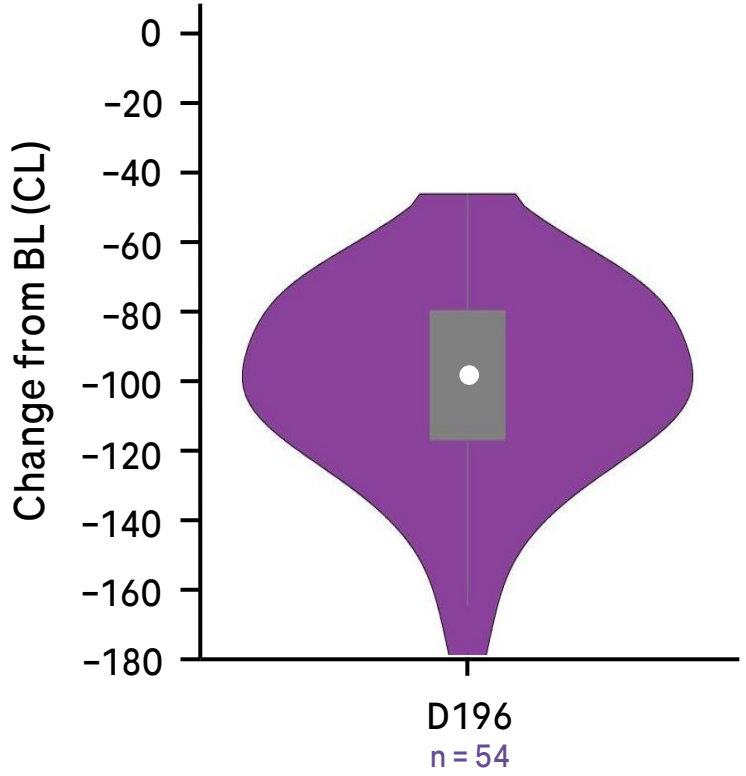
Nearly all participants near or below amyloid positivity threshold at trontinemab 3.6 mg/kg[a]

Amyloid PET trontinemab 3.6 mg/kg



Minimum −47 CL change from BL for trontinemab 3.6 mg/kg at D196

Substantial amyloid reduction in all participants



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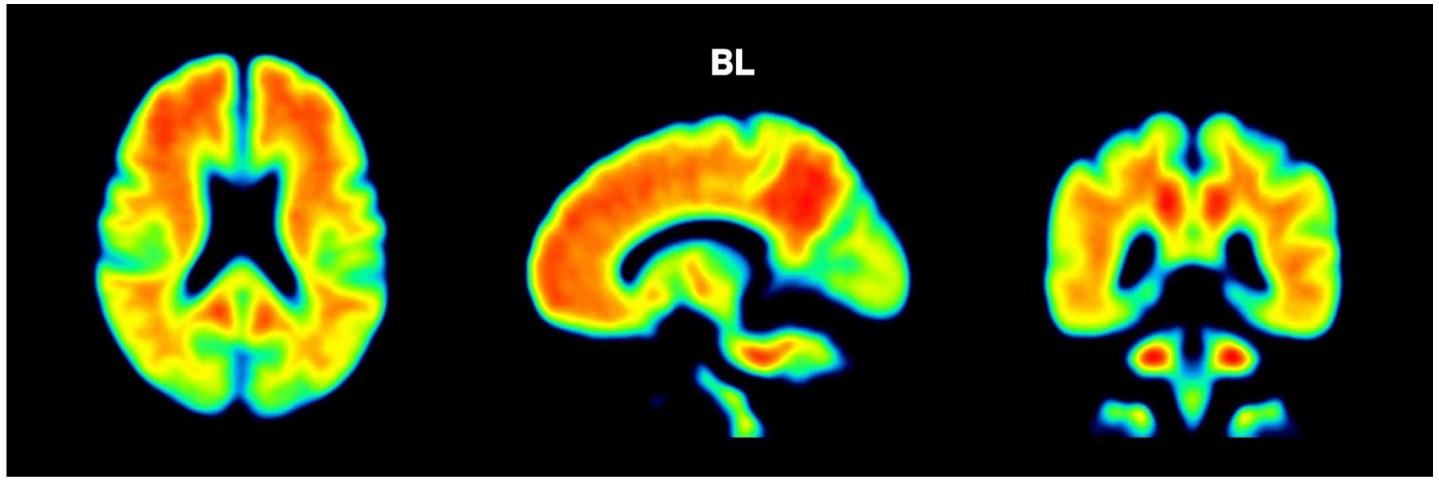
Cut-off date: 21 March 2025. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with CL). [a]Amyloid positivity threshold defined as ≤ 24 CL. The analysis is restricted to N = 54 trontinemab Cohort 4 (3.6 mg/kg) double blind completers from Part 1 and Part 2 combined who received the D196 PET scan. Nominal visits used for analysis. BL, baseline; CL, Centiloid; D, day; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Regional amyloid reduction of trontinemab 3.6 mg/kg (Part 1 + 2 combined)

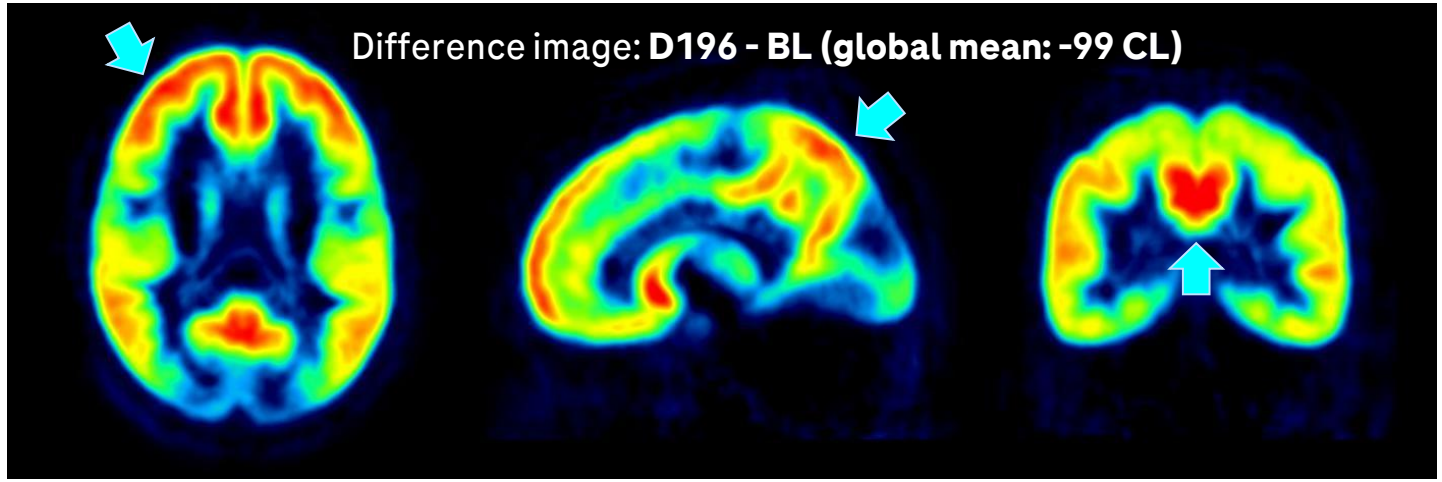
Extensive amyloid removal throughout the brain; greatest removal in frontal, parietal and cingulate regions



200 CL

0 CL

Trontinemab 3.6 mg/kg[a] Voxelwise average image at BL, D78, D196



-140 CL

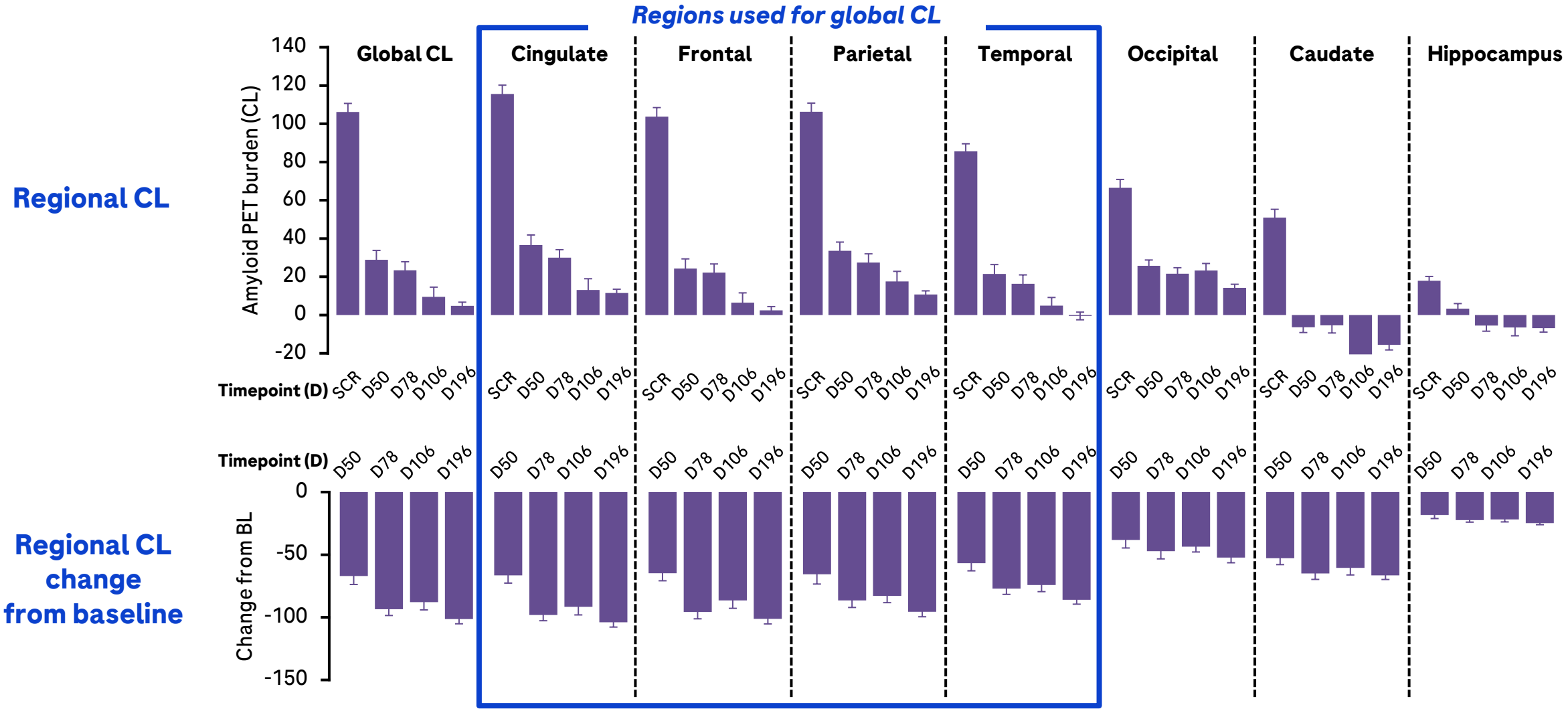
0 CL

Trontinemab 3.6 mg/kg[a] Voxelwise <u>difference image</u> showing amyloid reduction (global mean: -99 CL) at D196

Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. Florbetapir or florbetaben PET tracers were used (Freesurfer SUVR method, whole cerebellum reference, harmonized with CL). [a]Global CL transformation used to compute voxelwise average in MNI space from n = 54 Cohort 4 completers who received the D196 PET scan. Difference image calculated by subtracting average BL image from D196 average image. Global mean CL reduction of -99 CL at D196 obtained from MMRM CL analysis. BL, baseline; CL, Centiloid; D, day; MMRM, mixed models for repeated measures; MNI, Montreal Neurological Institute; SUVR, standardized uptake value ratio.

Quantitative regional CL change (Part 1 + 2 combined)

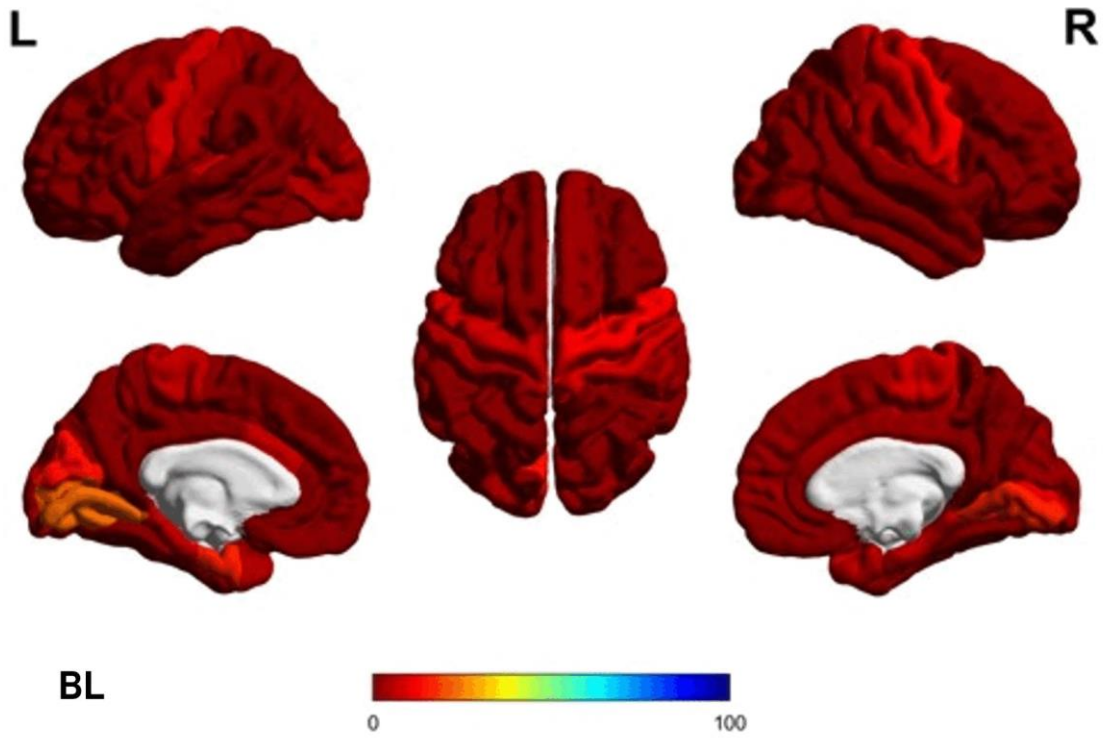
All neocortical regions show robust removal below 24 CL with trontinemab 3.6mg/kg[a]



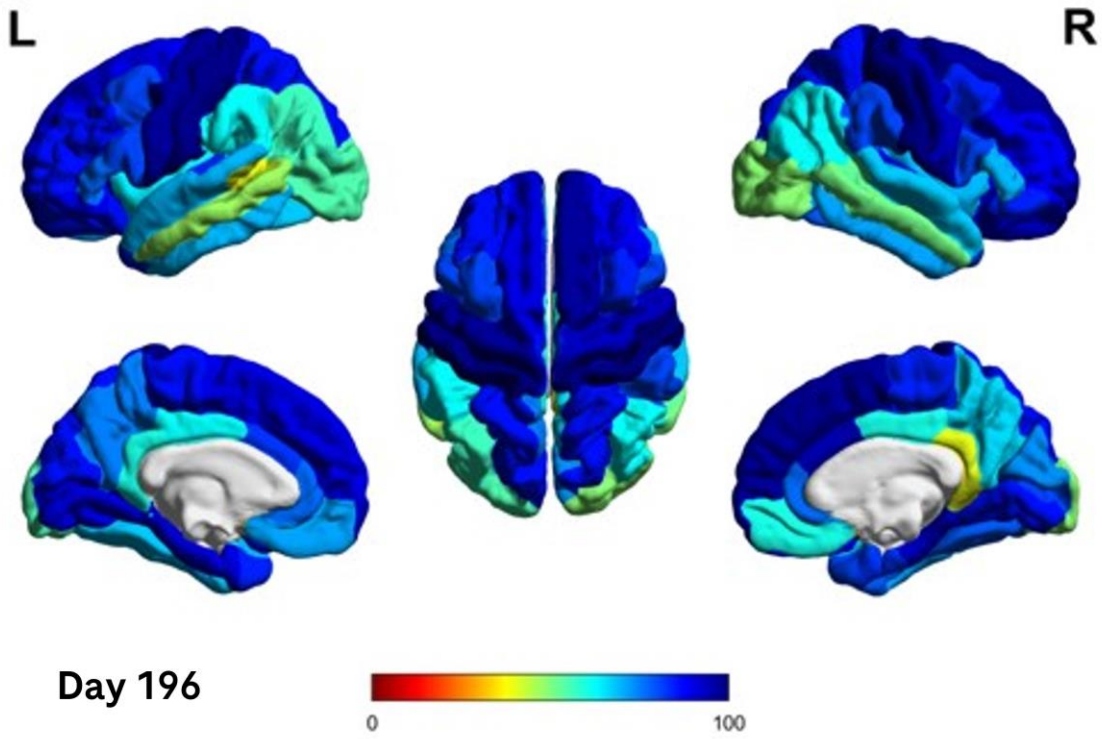
Trontinemab is an investigational product not approved for use in any market. [a]Amyloid positivity threshold is defined as ≤ 24 CL.
Cut-off date: 21 March 2025. Completer analysis of n = 54 Cohort 4 participants who received a D196 PET scan. Regional centiloid equations calculated from individual ROIs following global centiloid method (Klunk, et al 2014). BL, baseline; CL, Centiloid; D, day; ROIs, regions of interest; SCR, screening.

Regional CL negativity (Part 1 + 2 combined)

Extensive amyloid depletion in frontal, cingulate and parietal lobes at trontinemab 3.6 mg/kg



% Regional negativity at five timepoints after trontinemab treatment[a]



% Regional negativity after trontinemab treatment at D196[a]

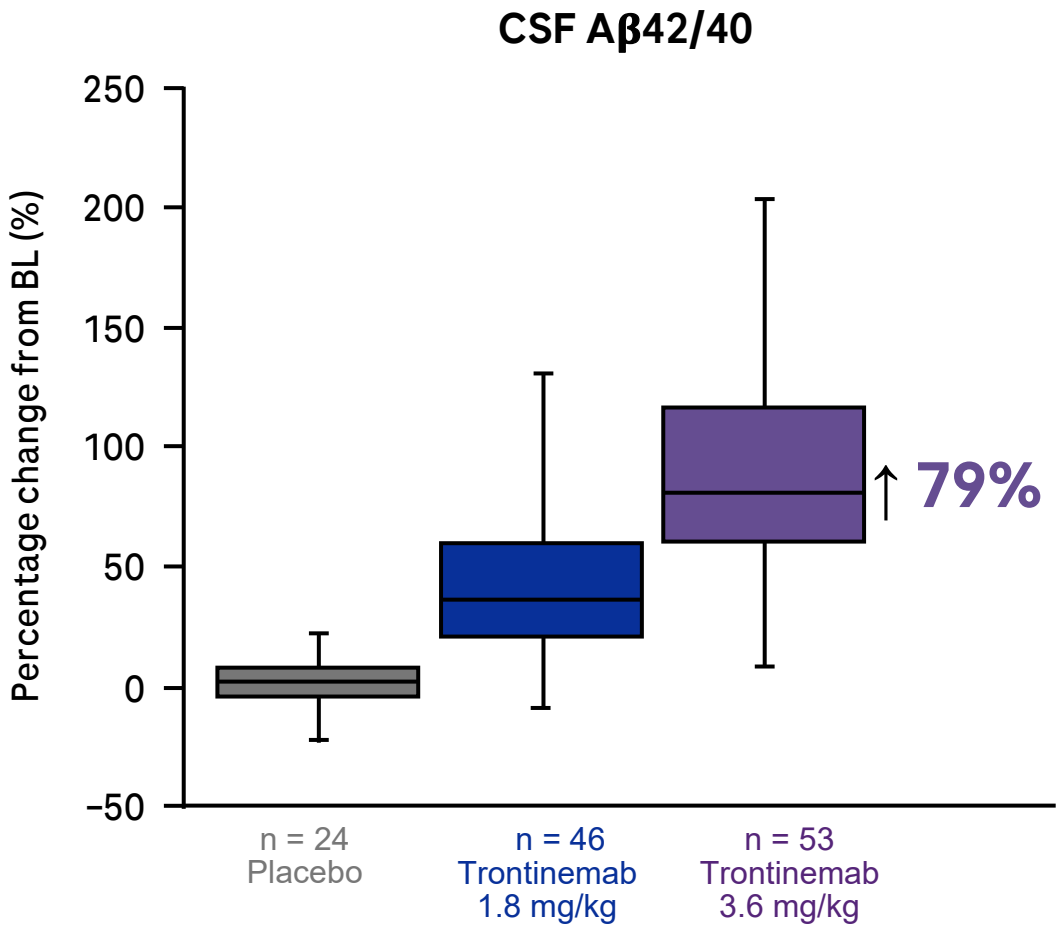
Trontinemab is an investigational product not approved for use in any market.

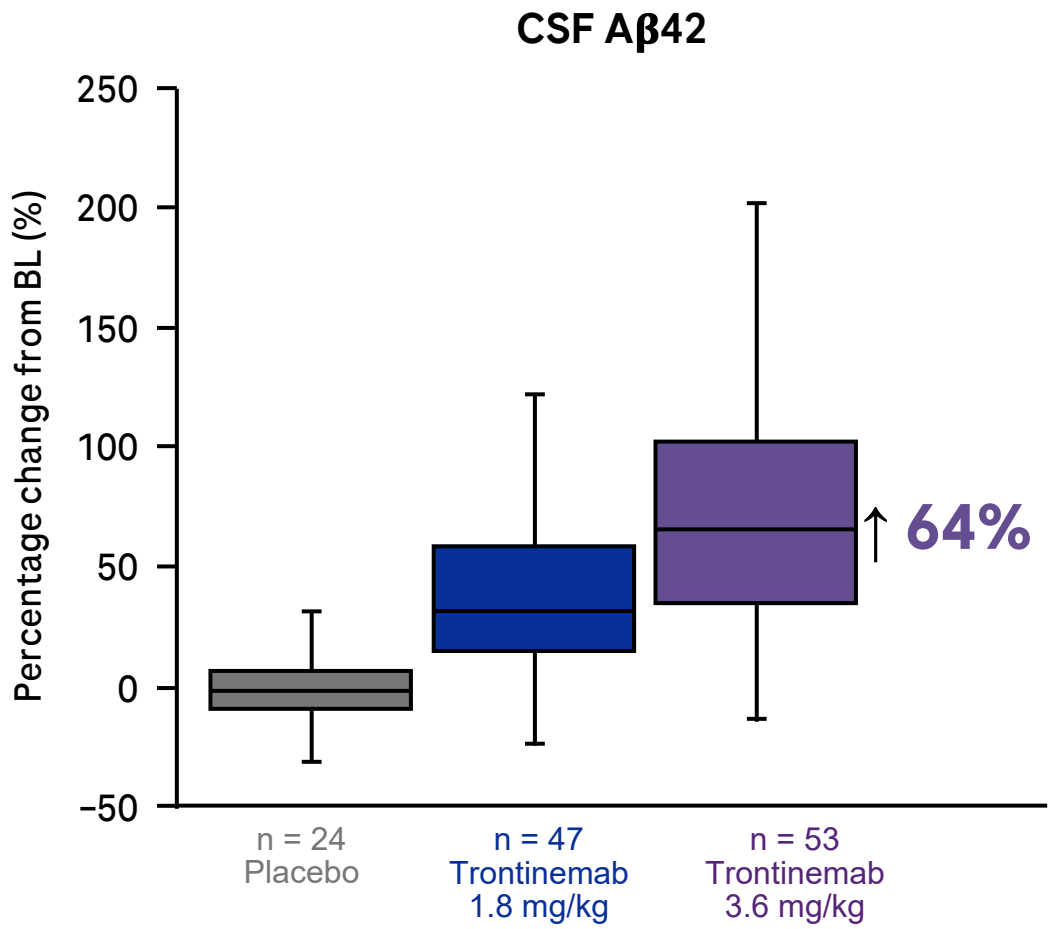
[a]Analysis were performed using regional SUVR where the negativity threshold was set for each tracer independently using the mean +2 SD of healthy controls participants available on the GAAIN website. Cohort 4 data is a mix of 10 florbetapir, 44 florbetaben longitudinal scans. D, day; GAAIN, Global Alzheimer's Association Interactive Network; SD, standard deviation; SUVR, standardized uptake value ratio.

Fluid biomarkers

CSF biomarker results at 25 weeks (Part 1 + 2 combined)

Pronounced effects of trontinemab on key amyloid biomarkers of disease in CSF



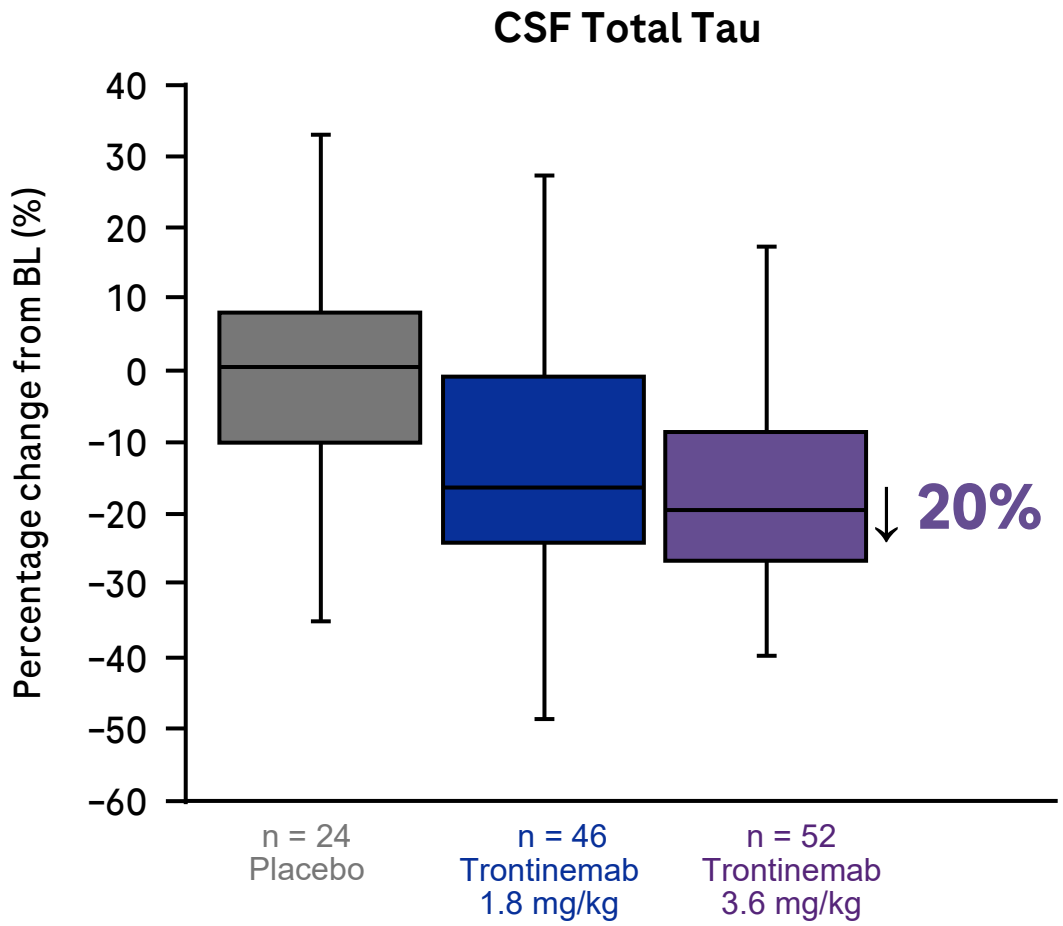


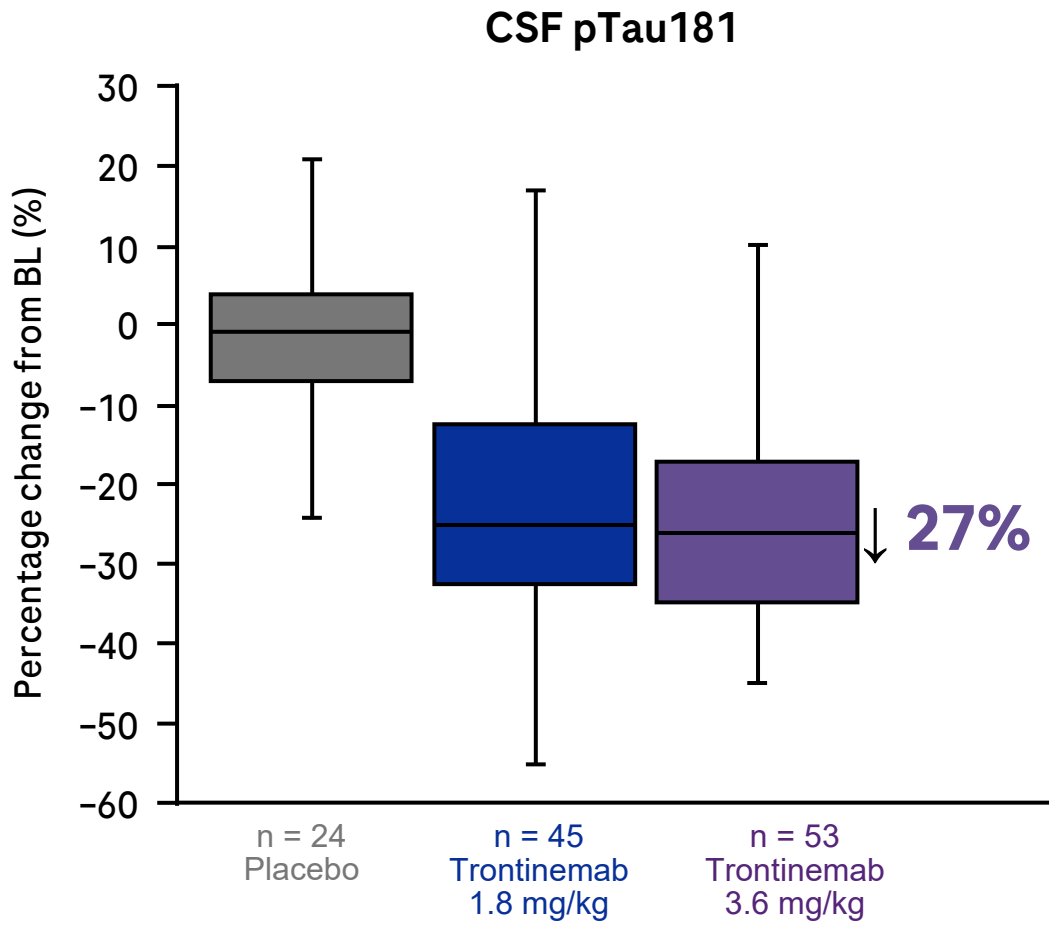
Findings are exploratory and no statistical analysis has been performed.

Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. CSF samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Median baseline values for Aß42/40: placebo 0.03, 1.8 mg/kg 0.03, 3.6 mg/kg 0.03; Aß42 (pg/mL): placebo 495.65, 1.8 mg/kg 449.80, 3.6 mg/kg 434.00. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted. Aβ, amyloid beta; CSF, cerebrospinal fluid.

CSF biomarker results at 25 weeks (Part 1 + 2 combined)

Pronounced effects of trontinemab on key downstream tau biomarkers of disease in CSF





Findings are exploratory and no statistical analysis has been performed.

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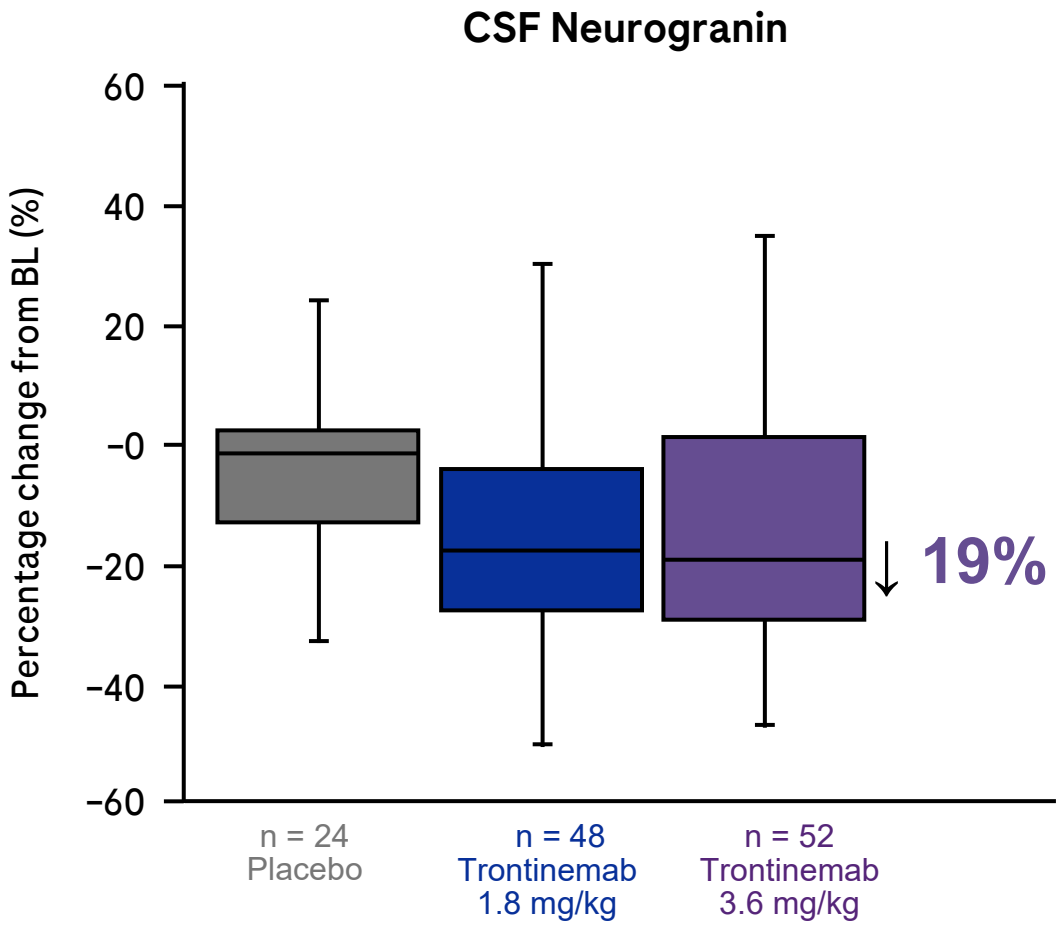
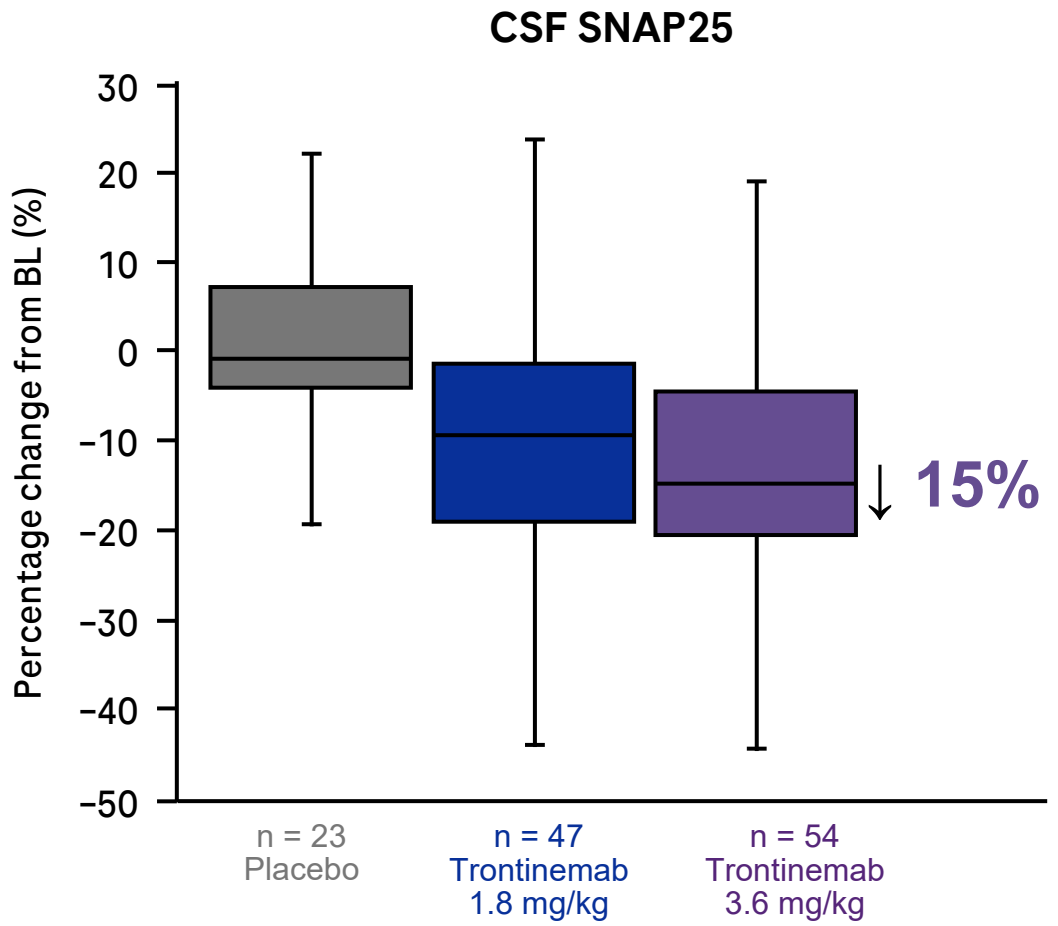
Cut-off date: 21 March 2025. Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. CSF samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Median baseline values for Total Tau (pg/mL): placebo 298.50, 1.8 mg/kg 329.00, 3.6 mg/kg 296.50. ptau181 (pg/mL): placebo 31.65, 1.8 mg/kg 33.30, 3.6 mg/kg 29.75. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted.
CSF, cerebrospinal fluid; pTau, phosphorylated tau.

CSF biomarker results at 25 weeks (Part 1 + 2 combined)

Effects of trontinemab on key downstream synaptic biomarkers of disease in CSF





Findings are exploratory and no statistical analysis has been performed.

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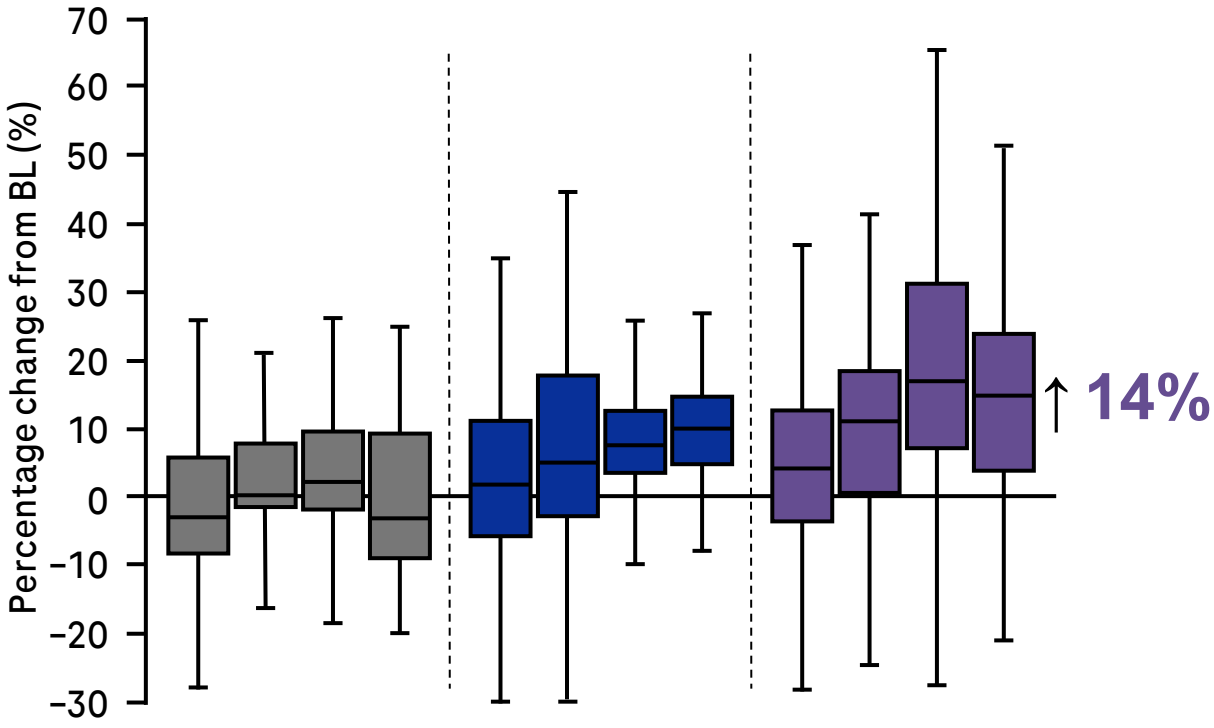
Cut-off date: 21 March 2025. Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. CSF samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Median baseline values for Neurogranin (pg/mL): placebo 1196.00, 1.8 mg/kg 1066.50, 3.6 mg/kg 931.00; SNAP25 (pg/mL): placebo 4010.00, 1.8 mg/kg 4065.00, 3.6 mg/kg 3550.00. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted. CSF, cerebrospinal fluid; SNAP25, synaptosomal-associated protein 25.

Plasma biomarker results (Part 1 + 2 combined)

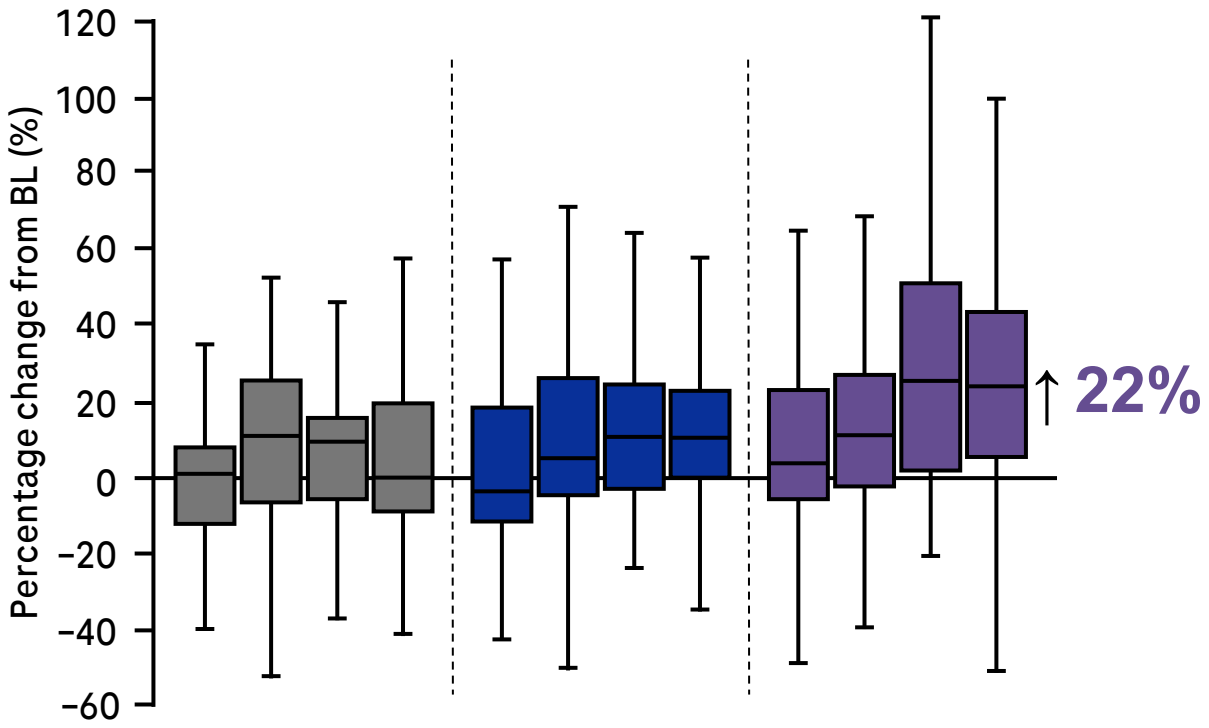
Dose and time-dependent increases in the Aβ42/40 ratio and Aβ42 in plasma

Plasma Aβ42/40



	Placebo				Trontinemab 1.8 mg/kg				Trontinemab 3.6 mg/kg			
Timepoint	D22	D78	D134	D183	D22	D78	D134	D183	D22	D78	D134	D183
n at visit	18	24	19	25	39	54	41	49	42	55	44	53

Plasma Aβ42



	Placebo				Trontinemab 1.8 mg/kg				Trontinemab 3.6 mg/kg			
Timepoint	D22	D78	D134	D183	D22	D78	D134	D183	D22	D78	D134	D183
n at visit	18	24	19	25	39	54	41	49	42	56	44	55

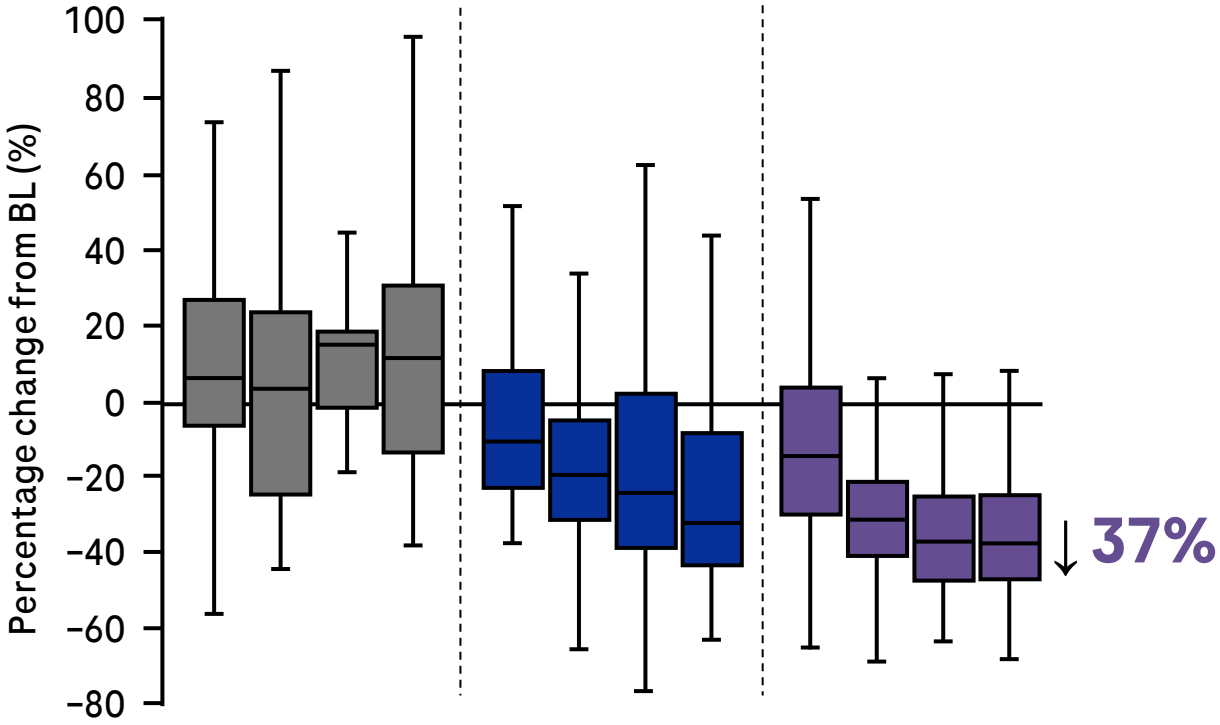
Findings are exploratory and no statistical analysis has been performed.

Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. Plasma samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. Median baseline values for Aβ42/40: placebo 0.09, 1.8 mg/kg 0.09, 3.6 mg/kg 0.09; Aβ42 (pg/mL): placebo 23.10, 1.8 mg/kg 23.85, 3.6 mg/kg 23.00. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted.
Aβ, amyloid beta; BL, baseline.

Plasma biomarker results (Part 1 + 2 combined)

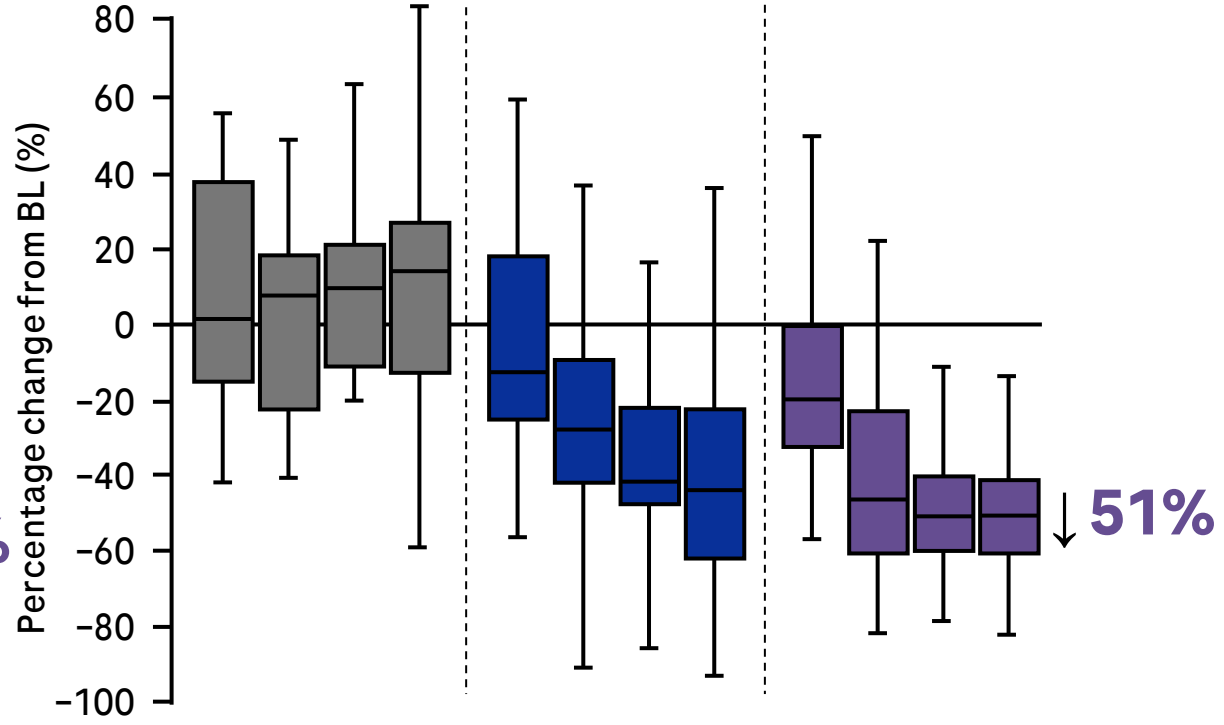
Early and large magnitude of effect in plasma pTau181 and pTau217 at 3.6 mg/kg after 6 months

Plasma pTau181



	Placebo				Trontinemab 1.8 mg/kg				Trontinemab 3.6 mg/kg			
Timepoint	D22	D78	D134	D183	D22	D78	D134	D183	D22	D78	D134	D183
n at visit	18	24	19	25	39	54	43	48	42	55	44	53

Plasma pTau217



	Placebo				Trontinemab 1.8 mg/kg				Trontinemab 3.6 mg/kg			
Timepoint	D22	D78	D134	D183	D22	D78	D134	D183	D22	D78	D134	D183
n at visit	18	24	19	25	39	54	42	48	42	55	44	55

Findings are exploratory and no statistical analysis has been performed.

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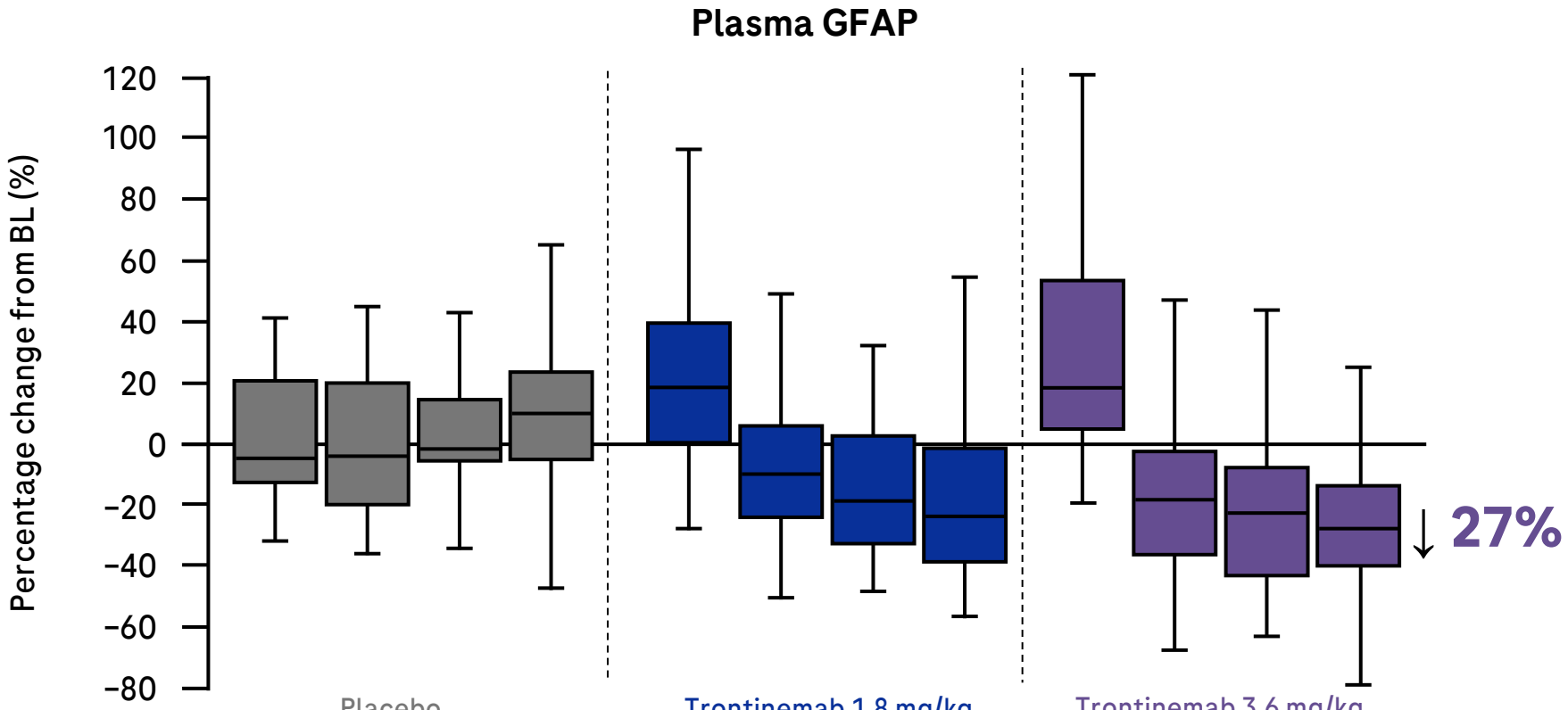
Cut-off date: 21 March 2025. Plasma samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. Median baseline values for pTau181 (pg/mL): placebo 1.34, 1.8 mg/kg 1.48, 3.6 mg/kg 1.51; pTau217 (pg/mL): placebo 0.64, 1.8 mg/kg 0.81, 3.6 mg/kg 0.78. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted.
BL, baseline; pTau, phosphorylated tau.

Plasma biomarker results (Part 1 + 2 combined)

GFAP reduction after initial transient increase may be related to glial activation during amyloid removal



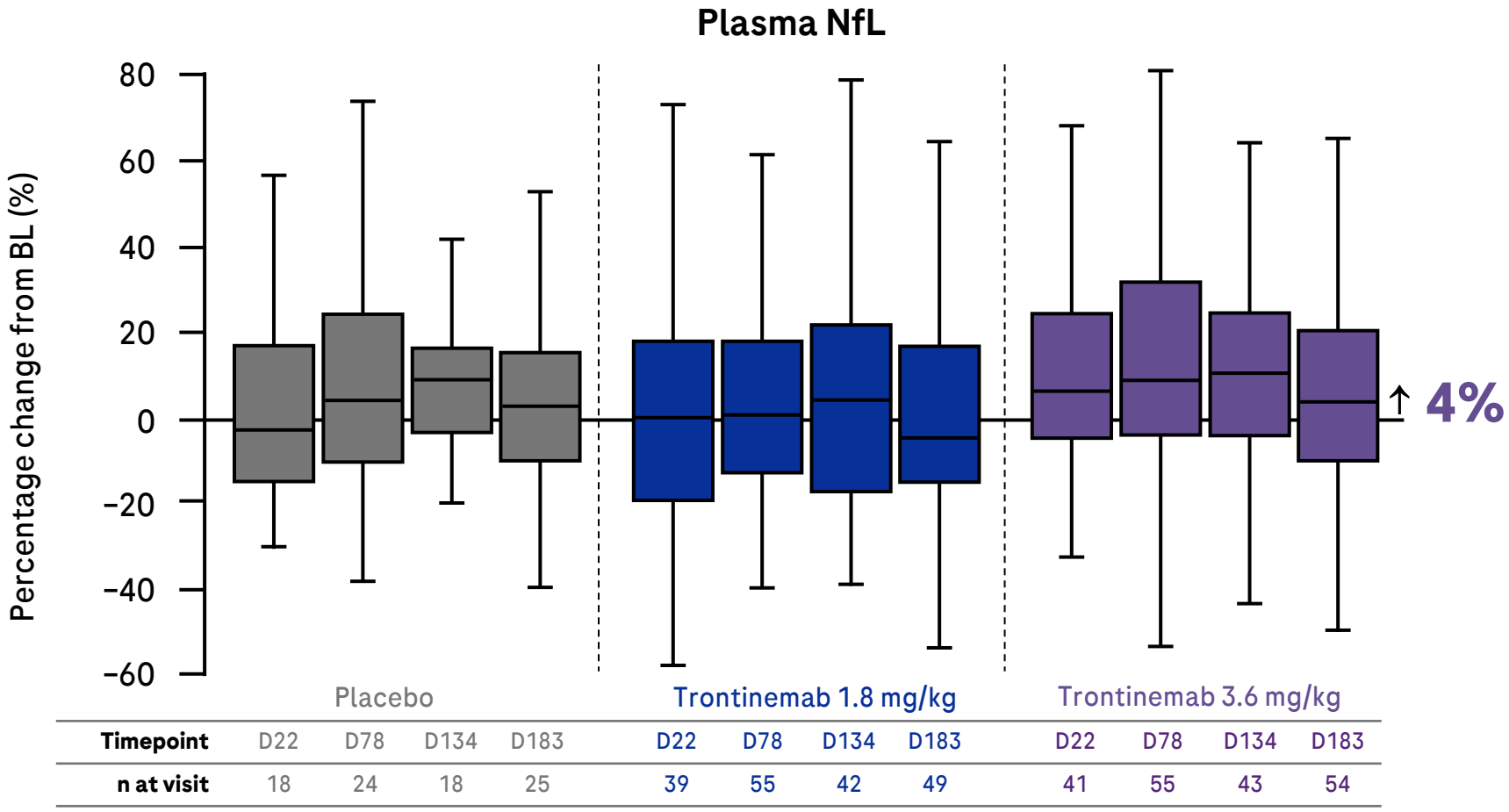
Timepoint	D22	D78	D134	D183	D22	D78	D134	D183	D22	D78	D134	D183
n at visit	17	24	18	25	39	55	39	49	42	55	44	54

Findings are exploratory and no statistical analysis has been performed.

Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. Plasma samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. Median baseline values for plasma GFAP (ng/mL): placebo 0.15, 1.8 mg/kg 0.17, 3.6 mg/kg 0.18. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted.
BL, baseline; GFAP, glial fibrillary acidic protein.

Plasma biomarker results (Part 1 + 2 combined)

No change observed in plasma NfL



Timepoint	D22	D78	D134	D183	D22	D78	D134	D183	D22	D78	D134	D183
n at visit	18	24	18	25	39	55	42	49	41	55	43	54

Findings are exploratory and no statistical analysis has been performed.

Trontinemab is an investigational product not approved for use in any market.
Cut-off date: 21 March 2025. Plasma samples were measured by the Roche NeuroToolKit, a portfolio of robust prototype assays, running on the fully automated Elecsys platform (Roche Diagnostics). Annotated percentages show the median percent change from baseline for 3.6 mg/kg at the latest displayed timepoint. Median baseline values for plasma NfL (pg/mL): placebo 3.04, 1.8 mg/kg 3.60, 3.6 mg/kg 3.76. Outliers more than 1.5 times the interquartile range above the third quartile or below the first quartile are not plotted.
BL, baseline; NfL, neurofilament light chain.

Summary

Results demonstrate rapid and robust amyloid plaque depletion at 3.6 mg/kg trontinemab

- Substantial amyloid reduction in all participants on trontinemab
- Average reduction of -99 CL at 28 weeks

Regional amyloid analysis shows robust amyloid removal throughout the brain

- Rapid and robust removal of amyloid in all neocortical regions below the 24 CL positivity threshold
- Some regional differences with greatest amyloid removal in frontal, cingulate and parietal lobes

Effects on key amyloid and downstream fluid biomarkers of AD pathology

- Consistent with strong effect observed on amyloid PET
- In CSF, pronounced effects on amyloid and tau biomarkers
- In plasma, effects on amyloid, tau and GFAP towards reduced pathology

Overall results support continued development of trontinemab

- Plan to initiate Phase III later in 2025

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Aβ, amyloid-beta; AD, Alzheimer's disease; CL, Centiloid; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; NFL, neurofilament light chain; PET, positron emission tomography; pTau, phosphorylated tau.