Anti-Aβ treatment effects on dominantly inherited AD: comparing neuropathology findings with biomarker outcomes from the DIAN-TU-001 trial of gantenerumab or solanezumab

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This study provides the best neuropathologic evidence to date of Aβ reduction in a trial of anti-Aβ monoclonal antibodies. Gantenerumab reduced Aβ burden in dominantly inherited AD in a dose-dependent manner without reducing tauopathy or gliosis.

INTRODUCTION

Clinical trials of anti-Aβ monoclonal antibodies in Alzheimer disease (AD) infer target engagement from Aβ positron emission tomography (PET) and/or fluid biomarkers such as cerebrospinal fluid (CSF) Aβ42/40. However, these biomarkers measure brain Aβ deposits indirectly and/or incompletely. Assessment of postmortem tissue is necessary to directly investigate treatment effects on brain Aβ deposits.

DIAN-Obs is a longitudinal observational study of dominantly inherited AD (DIAD); participants are at risk for or known to carry pathogenic variants in *PSEN1*, *PSEN2* or *APP*.

DIAN-TU-001 was a clinical trial in which participants at risk for DIAD were treated with placebo or an anti-Aβ antibody therapy (either gantenerumab or solanezumab) for up to ~4 years (Figure 1). Drug doses were increased mid-study, resulting in large differences in total dosage between participants who withdrew prior to or after dose escalation.

In both DIAN-Obs and DIAN-TU-001, participants were monitored for cognitive performance and AD biomarker changes in blood, CSF, MRI and Aβ-PET (^{11}C-PiB).

Aggregate analyses of the double-blind placebo-controlled period of DIAN-TU-001 found that neither gantenerumab nor solanezumab slowed cognitive decline and that, while gantenerumab treatment reduced brain Aβ burden, this removal was incomplete. Subsequent analyses of the open label extension period of DIAN-TU-001 suggest that a subset of participants treated longest with gantenerumab (an average of 8.4 years of exposure) showed a possible benefit: approximately 50% slowing of dementia progression (AAIC 2024 Developing Topic Sessions Presentation #94832).

Since DIAN-TU-001 trial inception, a small number of participants expired (not related to therapy) and underwent brain donation. These brains were examined according to the protocol of the DIAN-Obs/DIAN-TU Neuropathology Core Laboratory.

In this study, we evaluated the hypothesis that gantenerumab and/or solanezumab treatment in DIAN-TU-001 reduced brain Aβ burden and introduced associated changes in tauopathy and neuroinflammation, by comparing each drug-treated DIAN-TU-001 autopsy group to a similar control group derived from brain donors from DIAN-TU-001 and the DIAN-Obs study.

Towards this end, we evaluated CSF biomarker and Aβ PET SUVR measurements of these select participants, and results from quantitative digital immunohistochemistry of 10 brain areas for Aβ deposits, tauopathy, astrocytosis, and microgliosis.

Fig 1. DIAN-TU AD Secondary Prevention Trial Platform

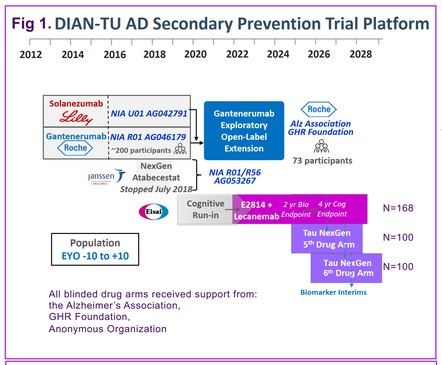
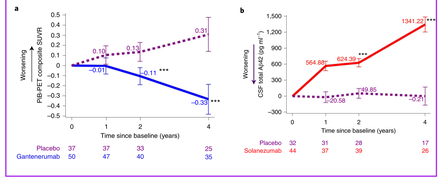
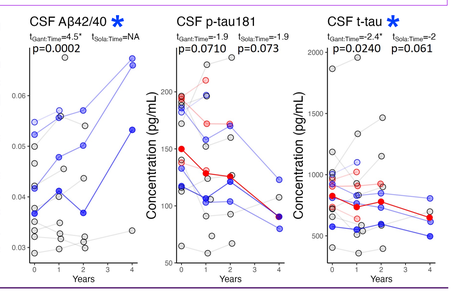


Figure 2. In aggregate analyses, neither gantenerumab nor solanezumab slowed cognitive decline during the double-blind placebo-controlled period of the DIAN-TU-001 trial (right), but PiB-PET and CSF Aβ42 suggested partial brain Aβ removal by gantenerumab (below).



METHODS & RESULTS

Figure 3. CSF Aβ42/40 increased, CSF t-tau decreased, in gantenerumab vs. controls. Linear mixed-effects models of the form CSF~Drug*Time+(1|Participant) were used to estimate statistical differences in longitudinal change of CSF biomarkers between either **gantenerumab** or **solanezumab** treatment arms and the control group. $t_{Gant:Time}$ denotes the t-value of the Gant:Time interaction. Asterisks denote p-values<0.05 associated with $t_{Gant:Time}$; no $t_{Sola:Time}$ interaction was significant. No solanezumab arm participants had CSF Aβ42/40. Five control group participants did not have longitudinal CSF measurements.



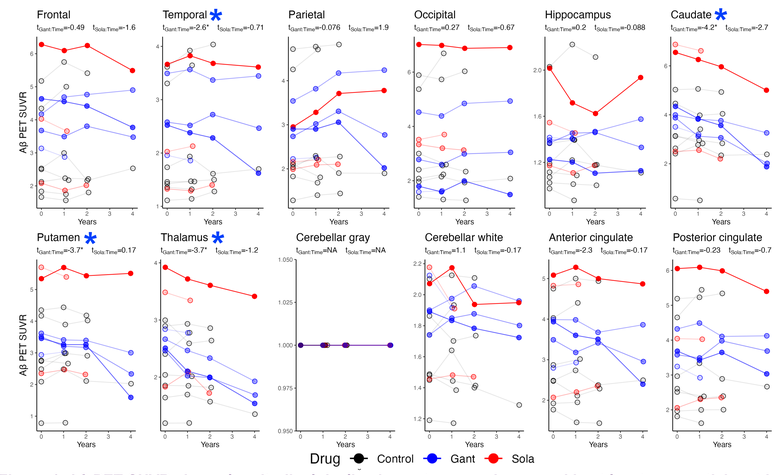


Figure 4. Aβ PET SUVR shows longitudinal decline in gantenerumab arm and in at least one participant in the solanezumab arm. Linear mixed-effects models, nomenclature, and figure labeling as described above for Figure 3. P-values were adjusted by the Benjamini-Hochberg procedure.

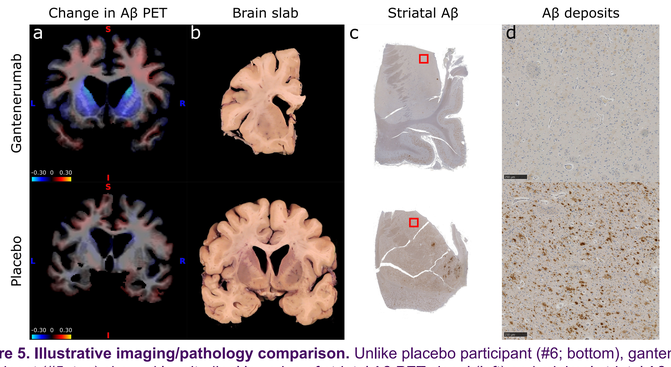


Figure 5. Illustrative imaging/pathology comparison. Unlike placebo participant (#6; bottom), gantenerumab participant (#5; top) showed longitudinal lowering of striatal Aβ PET signal (left) and minimal striatal Aβ by IHC.

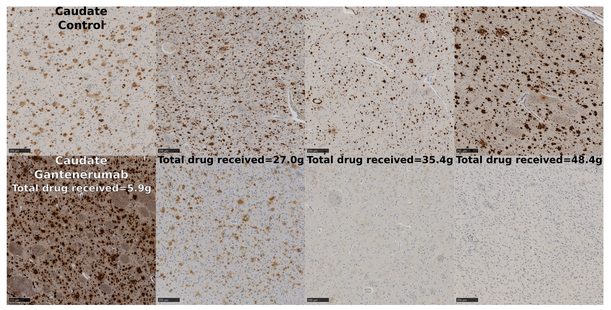


Figure 6. Aβ deposits in caudate show dose-response to gantenerumab. Fields as in Fig 5 (red box) from IHC slides in Fig 7. Controls matched by family mutation and age at death.

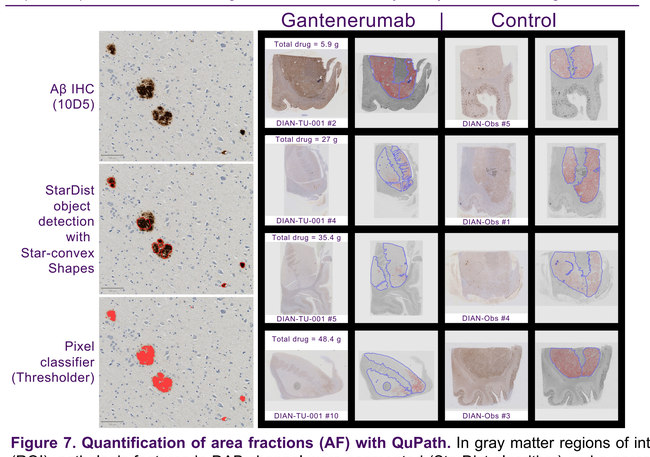


Figure 7. Quantification of area fractions (AF) with QuPath. In gray matter regions of interest (ROI), pathologic features in DAB channel were segmented (StarDist algorithm) and a percentile-based pixel thresholder was used to calculate AF (% pixels with intensity above threshold in ROI).

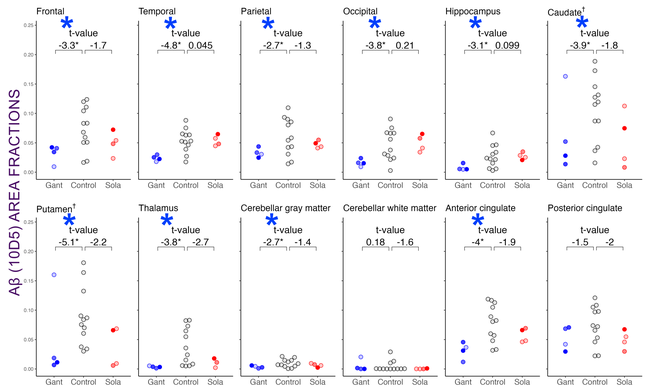


Figure 8. Aβ area fractions are significantly lower in gantenerumab arm vs control group. Welch two sample t-tests were used to estimate statistical differences in postmortem neuropathology between either **gantenerumab** or **solanezumab** arms and the **control** group.

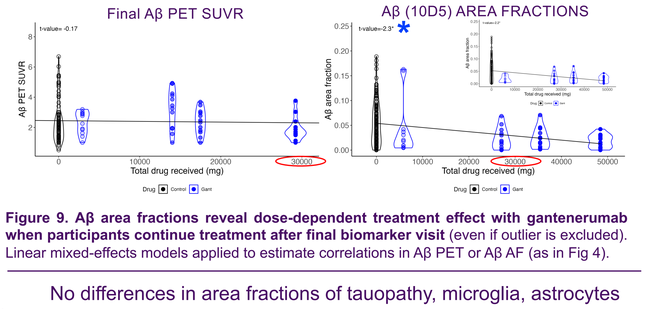


Figure 9. Aβ area fractions reveal dose-dependent treatment effect with gantenerumab when participants continue treatment after final biomarker visit (even if outlier is excluded). Linear mixed-effects models applied to estimate correlations in Aβ PET or Aβ AF (as in Fig 4).

No differences in area fractions of tauopathy, microglia, astrocytes

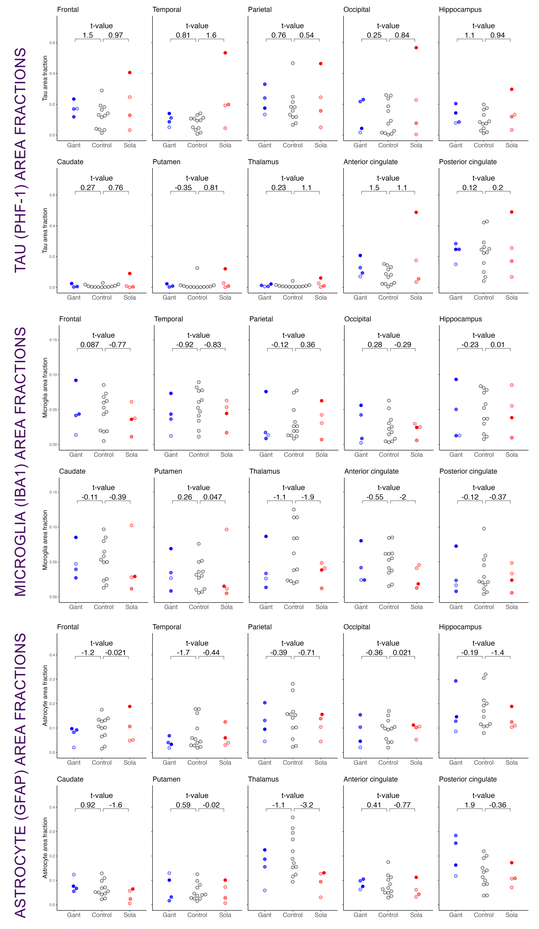


Figure 10. AFs of tauopathy (PHF-1 IHC), microglia (Iba1), astrocytes (GFAP) show no evidence of treatment effects with gantenerumab or solanezumab versus controls. Welch two sample t-tests were performed as described in Fig 8.

Table 1. Participant characteristics and postmortem neuropathologic findings

	Sex	*APOE*	Family mutation	Mean mutation age of onset	Age at baseline	CDR® at baseline	Drug	Days on low dose	Max low dose (mg)	Days on high dose	Max high dose (mg)	Drug by final PET (mg)	Drug by final CSF (mg)	Total drug received (mg)	Age at death	Final CDR®	Interval last dose to death (years)	Thal phase	Braak NFT stage	CERAD NP score	CAA	LBD	Additional postmortem findings
DIAN-TU-001																							
1	M	23	*PSEN1*	40-50	50-60	1	Sola	507	400	0	N/A	N/A	4800	7200	50-60	3	2	5	V	3	3	Amy	0
2***	M	34	*APP*	40-50	40-50	0.5	Gant	696	225	0	N/A	2925	2925	5850	50-60	2	2	5	VI	3	1-2	Limbic	Arteriosclerosis 2-3
3***	M	33	*PSEN1*	40-50	50-60	1	Sola	1402	400	0	N/A	10400	10400	20400	60-70	2	1	5	VI	3	3	0	Arteriosclerosis 1
4	M	34	*PSEN1*	40-50	40-50	0.5	Gant	1255	225	520	1200	14010	14010	27045	40-50	3	2	5	VI	3	1-2	Amy	0
5	M	23	*PSEN1*	40-50	40-50	1	Gant	904	225	1117	900	17475	17475	35400	50-60	3	0	3	VI	3	2	0	0
6	F	44	*PSEN1*	50-60	50-60	0.5	Placebo	0	0	0	0	0	0	0	50-60	3	N/A	5	VI	3	3	Limbic	TDP-43 1; cortical microinfarct
7	F	33	*PSEN1*	20-30	30-40	1	Sola	421	400	0	N/A	6000	5200	6400	40-50	3	3	5	VI	3	1; 3 in cbl	Neo	0
8*	M	33	*PSEN1*	20-30	30-40	1	N/A	0	0	0	0	N/A	N/A	0	30-40	3	N/A	5	VI	3	1-2; 3 in cbl	Amy	Acute/subacute perivasc wm hemorrhages
9	F	33	*PSEN1*	30-40	30-40	1	Sola	784	400	645	1600	46800	46800	48400	40-50	3	1	5	VI	3	1	Amy	Arteriosclerosis 1
10	M	34	*PSEN1*	60-70	50-60	0.5	Gant	787	225	1068	1200	29220	29220	48420	60-70	3	2	5	VI	3	2-3	Limbic	TDP-43 2; ARTAG; arteriosclerosis 1-2
DIAN-Obs																							
1**	M	N/A	*PSEN1*	40-50	N/A	N/A	N/A	0	N/A	0	N/A	N/A	N/A	0	40-50	3	N/A	5	VI	3	2-3	0	Arteriosclerosis 1
2	M	44	*PSEN1*	30-40	40-50	0.5	N/A	0	N/A	0	N/A	N/A	N/A	0	40-50	3	N/A	5	VI	3	2	Neo	Glioblastoma; arteriosclerosis 1
3**	F	N/A	*PSEN1*	40-50	N/A	N/A	N/A	0	N/A	0	N/A	N/A	N/A	0	60-70	3	N/A	5	VI	3	2-3	Neo	Arteriosclerosis 1-2
4	F	23	*PSEN1*	40-50	40-50	2	N/A	0	N/A	0	N/A	N/A	N/A	0	40-50	3	N/A	5	VI	3	1	0	0
5	M	44	*APP*	50-60	50-60	1	N/A	0	N/A	0	N/A	N/A	N/A	0	50-60	3	N/A	5	VI	3	2	Limbic	Arteriosclerosis 1
6	F	34	*PSEN1*	30-40	30-40	1	N/A	0	N/A	0	N/A	N/A	N/A	0	40-50	3	N/A	5	VI	3	2-3	Limbic	0
7	M	33	*PSEN1*	40-50	50-60	0.5	N/A	0	N/A	0	N/A	N/A	N/A	0	50-60	3	N/A	5	VI	3	2-3	0	Arteriosclerosis 1
8	M	33	*PSEN1*	50-60	50-60	3	N/A	0	N/A	0	N/A	N/A	N/A	0	60-70	3	N/A	5	VI	3	1	0	Arteriosclerosis 1
9	F	33	*PSEN1*	40-50	40-50	0.5	N/A	0	N/A	0	N/A	N/A	N/A	0	40-50	3	N/A	5	VI	3	2	Olf	0
10	M	33	*PSEN1*	40-50	40-50	0.5	N/A	0	N/A	0	N/A	N/A	N/A	0	50-60	3	N/A	5	VI	3	2-3	0	Thromboses, infarcts

*This participant was part of the DIAN-TU Cognitive Run-In (CRI) and did not ultimately enroll in a drug arm and thus has limited antemortem data available. **These participants were family members of DIAN-Obs participants who consented to brain donation but did not otherwise participate in the study and thus have limited antemortem data available. ***No CDR® was available for these participants immediately prior to death; their "Final CDR" reflects last clinical assessment before death. †Abbreviations: APOE=apolipoprotein E, NFT=neurofibrillary tangle; NP=neuritic plaque; CAA=cerebral amyloid angiopathy; LBD=Lewy body disease (Amy=amygdala predominant; Limbic=limbic predominant, brainstem-sparing; Neo=diffuse neocortical); wm=white matter

CONCLUSIONS / DISCUSSION

- **Gantenerumab treatment in DIAN-TU-001 reduced Aβ deposits (incompletely) in many brain areas in a dose-dependent manner, with no apparent affect on IHC area fractions of tauopathy, microglia, or astrocytes.**
- **Earlier intervention and stronger treatments may be required for more complete Aβ plaque removal**

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