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RESEARCH ARTICLE

Evaluation of dose-dependent treatment effects after mid-trial dose escalation in biomarker, clinical, and cognitive outcomes for gantenerumab or solanezumab in dominantly inherited Alzheimer's disease

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Abstract

Introduction: While the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) was ongoing, external data suggested higher doses were needed to achieve targeted effects; therefore, doses of gantenerumab were increased 5-fold, and solanezumab was increased 4-fold. We evaluated to what extent mid-trial dose increases produced a dose-dependent treatment effect.

Methods: Using generalized linear mixed effects (LME) models, we estimated the annual low- and high-dose treatment effects in clinical, cognitive, and biomarker outcomes.

Results: Both gantenerumab and solanezumab demonstrated dose-dependent treatment effects (significant for gantenerumab, non-significant for solanezumab) in their respective target amyloid biomarkers (Pittsburgh compound B positron emission tomography standardized uptake value ratio and cerebrospinal fluid amyloid beta 42), with gantenerumab demonstrating additional treatment effects in some downstream biomarkers. No dose-dependent treatment effects were observed in clinical or cognitive outcomes.

Conclusions: Mid-trial dose escalation can be implemented as a remedy for an insufficient initial dose and can be more cost effective and less burdensome to participants than starting a new trial with higher doses, especially in rare diseases.

KEYWORDS
autosomal dominant Alzheimer's disease, Dominantly Inherited Alzheimer Network, dose escalation, gantenerumab, solanezumab

Highlights

- We evaluated the dose-dependent treatment effect of two different amyloid-specific immunotherapies.
- Dose-dependent treatment effects were observed in some biomarkers.
- No dose-dependent treatment effects were observed in clinical/cognitive outcomes, potentially due to the fact that the modified study may not have been powered to detect such treatment effects in symptomatic subjects at a mild stage of disease exposed to high (or maximal) doses of medication for prolonged durations.

1 | INTRODUCTION

The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)-001 is a phase II/III randomized, double-blind, placebo-controlled, cognitive endpoint, international study of potential disease-modifying therapies (gantenerumab and solanezumab) in individuals with dominantly inherited Alzheimer's disease (DIAD) mutations. The design[1] of this trial incorporated several innovative strategies such as: a platform trial with a master protocol to concurrently and sequentially investigate multiple drugs,[1,2] a shared placebo group between active arms allowing for a 3:1 randomization in each arm, extended follow-up with a common-close design for all participants instead of a fixed study duration (4 years up to 7 years in the placebo-controlled period), the use of a multivariate cognitive endpoint; an interim biomarker analysis, and dose escalation. The main findings of the primary and secondary analyses were a lack of cognitive benefit but significant amyloid beta (Aβ) target engagement of gantenerumab (fibrillar Aβ) and solanezumab (soluble Aβ).[3] In addition, gantenerumab had a significant effect on downstream biomarkers (e.g., decreased cerebrospinal fluid [CSF] measures of phosphorylated tau [p-tau], total tau, and neurofilament light chain [NfL]).[3] Based on these findings, the trial continued in an exploratory open label extension for gantenerumab at the higher dose used in the double-blind period. The goal of this report is to: (1) present details of the dose escalation procedure and (ii) evaluate and quantify the dose-dependent effects of gantenerumab and solanezumab in clinical, cognitive, imaging, and CSF biomarker endpoints. We hypothesized dose-dependent treatment benefits for gantenerumab and solanezumab in clinical, cognitive, imaging, and CSF biomarker outcomes.

2 | METHOD

2.1 | Study oversight

The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines and had ethics committee approval at each participating site. All participants provided written informed consent.

2.2 | Study participants

The details about the trial participants have been reported previously.[3] Briefly, 194 participants enrolled in DIAN-TU-001, of whom 144 were DIAD mutation carriers (52 on gantenerumab, 52 on solanezumab, and 40 on placebo). These participants were either cognitively normal (Clinical Dementia Rating [CDR= 0]) or had early-stage disease (CDR 0.5 or 1 representing very mild or mild dementia) at enrollment.

2.3 | Dose escalation

The initial dose in the DIAN-TU-001 study was 225 mg of gantenerumab administered subcutaneously every 4 weeks, and 400 mg of solanezumab administered intravenously every 4 weeks. Midway through the DIAN-TU-001 study, results of concurrent phase II and III trials with the same drugs in sporadic Alzheimer's disease (AD) were made public,[4,5] and indicated the initial doses for both drugs in

the DIAN-TU-001 trial were unlikely to yield sufficient reduction in amyloid deposition or demonstrate significant clinical/cognitive benefit at these doses. Therefore, dose escalation was proposed as a potential remedy. After obtaining regulatory approval, all active participants in the study at that time initiated dose escalation. Because amyloid-related imaging abnormalities (ARIAs) were more common for gantenerumab compared to solanezumab in previous studies, the dose escalation and safety magnetic resonance imaging (MRI) schedules were drug specific: the gantenerumab dose was increased stepwise every 8 weeks to a maximum dose of 1200 mg (titrating up after two doses at each of the following dose levels: 225, 450, 675, and 900 mg), or the highest dose that an individual can tolerate, with safety MRIs scheduled at each step (Table 1). The solanezumab dose was increased stepwise every 4 weeks to a maximum dose of 1600 mg (titrating up from 400 mg to 800 mg every 4 weeks for two doses, to 1600 mg every 4 weeks), or the highest dose that an individual can tolerate, with a safety MRI scheduled after the second dose of 800 mg (Table 1).

2.4 | Clinical, cognitive, imaging, and CSF biomarker outcomes

The clinical outcomes analyzed included the CDR-Sum of Boxes[6] (CDR-SB) and Functional Assessment Scale (FAS)[7]; the cognitive outcomes included the Mini-Mental State Examination (MMSE),[8] the Wechsler Memory Scale-Revised Logical Memory Delayed Recall Test (Logical Memory),[9] the Wechsler Adult Intelligence Scale Digit Symbol Substitution Test (Digit Symbol),[9] and the International Shopping List Test (ISLT) Delayed Recall score;[10,11] the imaging and CSF biomarker outcomes included Pittsburgh compound B positron emission tomography (PiB-PET) composite standardized uptake value ratio (SUVR), fluorodeoxyglucose (FDG)-PET SUVR, MRI-derived volumetrics, CSF total Aβ42 (defined as free plus bound Aβ42) for solanezumab, CSF Aβ42 for gantenerumab, CSF total tau, CSF p-tau181, and CSF NfL. Methods used for imaging biomarkers were described previously.[12–14] CSF biomarker methods are described in the supporting information.

2.5 | Statistical analysis plan

Because dose escalation was initiated while the study was ongoing and at different times for gantenerumab and solanezumab arms, each participant had a variable duration of exposure to the high doses (defined as any dose higher than the initial dose) depending on how long that individual had already been on the low dose (the initial dose). In some instances, participants withdrew from the study before dose escalation. To accommodate the individual-specific low- and high-dose treatment durations, generalized linear mixed effects (LME) models were used to estimate the annual rates of change in each outcome during the low- and high-dose periods simultaneously in a single model including the gantenerumab, solanezumab, and placebo arms.[15] The placebo arm included the pooled placebos from both gantenerumab and solanezumab. Statistical inference on treatment efficacy in each outcome was made by comparing the annual rates of change of each treatment arm to that of the placebo arm, whereas the gantenerumab arm and the solanezumab arm were not to be compared per protocol. For clinical and cognitive measures, all data collected until the conclusion of this common-close study were included in the model, whereas for biomarker measures, data were collected only up to year 4. The LME models included random intercepts and random slopes at the individual level to account for the correlation among repeated measures. The variances of these random effects and the residual variance were modeled separately for asymptomatic (CDR 0 at baseline) and symptomatic (CDR 0.5–1 at baseline) participants (Statistical Supplemental Materials for details). The normality assumption was examined using the residual plots from the LME models. When the assumption was determined to not be sufficiently met, a log transformation was applied.

All analyses were conducted with the use of SAS software, version 9.4. Nominal *P*-values were presented from two-sided *t*-tests with type I error of 0.05. All confidence intervals (CIs) were 95% CIs.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Publications related to dose escalation for Alzheimer's disease clinical trials have been identified and properly cited.
2. **Interpretation**: The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)-001 platform trial successfully and safely implemented a dose escalation procedure for both study drug arms based on results from concurrent studies in sporadic AD while the trial was still ongoing. To optimize participant safety and characterize the safety profile of the higher doses, participants were carefully monitored during dose escalation. Compared to the initial dose, the high doses led to larger treatment effects in each drug's biomarker of target engagement of amyloid beta (Aβ; 90% more decrease in Pittsburgh compound B positron emission tomography standardized uptake value ratio with high-dose gantenerumab, 41% more increase in total Aβ42 with high-dose solanezumab).
3. **Future directions**: Future AD clinical trials with an insufficient initial dose may use the DIAN-TU approach to conduct dose escalation during the trial as a remedy. Additional measures may be needed to facilitate the treatment effect evaluation after mid-trial dose escalation such as "re-start the clock" of the follow-up duration to increase the high-dose exposure and enroll additional participants to account for the early dropouts.

TABLE 1 DIAN-TU-001 gantenerumab/solanezumab dose escalation and safety MRI schedule

	Titration step 1	Titration step 2	Titration step 3	Titration step 4	Titration step 5
Gantenerumab	• Dose 1: 450 mg • Dose 2: 450 mg • Safety MRI: 1 week after 2nd 450 mg dose, before increase to 675 mg	• Dose 1: 675 mg • Dose 2: 675 mg • Safety MRI: 1 week after 2nd 675 mg dose, before increase to 900 mg	• Dose 1: 900 mg • Dose 2: 900 mg • Safety MRI: 1 week after 2nd 900 mg dose, before increase to 1200 mg	• Dose 1: 1200 mg • Dose 2: 1200 mg • Dose 3: 1200 mg • Safety MRI: 1 week after 3rd 1200 mg dose • Dose 4: 1200 mg • Dose 5: 1200 mg • Dose 6: 1200 mg • Safety MRI	• 1200 mg dose every 4 weeks • Safety MRI: 1 week after every 6th dose; safety MRI must occur regardless of when annual MRI is scheduled
Solanezumab	• Dose 1: 800 mg • Dose 2: 800 mg • Safety MRI: 1 week after 2nd 800 mg dose, before increase to 1600 mg	• 1600 mg dose every 4 weeks			

Abbreviations: DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; MRI, magnetic resonance imaging.

3 | RESULTS

3.1 | Demographics

The demographics at baseline were reported previously[3] and were well balanced among the gantenerumab arm, the solanezumab arm, and the placebo arm. Gantenerumab started dose escalation an average of 1.8 (standard deviation [SD] 0.61) years after baseline, and 47 out of 52 (90%) had at least one high-dose administration with an average duration of 2.4 (SD 0.55) years; solanezumab started an average of 3.2 (SD 0.67) years after baseline, and 37 out of 52 (71%) received at least one high-dose administration with an average duration of 1.3 (SD 0.42) years. Of the 52 gantenerumab participants, 43 (83%) received an average of 26.3 (SD 9.9) administrations of the maximum dose (1200 mg) and 37 (71%) of the 52 solanezumab participants received an average of 18.6 (SD 4.8) administrations of the maximum dose (1600 mg). Table 2 shows the differences in clinical/cognitive outcomes at baseline and at visits closest (either before or after) to dose escalation. Table S1 in supporting information presents the clinical/cognitive/biomarker outcomes before the dose escalation (the last visit on low dose) and after the dose escalation (the last visit on high dose).

3.2 | Low- and high-dose treatment effects for clinical and cognitive outcomes

The estimated annual treatment effects for cognitive and clinical outcomes (defined as the difference in the annual change between the treatment group and the placebo group) before and after dose escalation are shown in Figure 1 and Table S2 in supporting information. Compared to the placebo, neither the low- nor the high dose of either study drug arm yielded significant improvement on any of the cognitive or clinical outcomes except that the gantenerumab low dose slightly improved the Digit Symbol Substitution Test by 1.89/year with 95% CI 0.11, 3.68 compared to the placebo arm (Figure 1 and Table S2). Analyses of participants who completed at least 4 years of treatment showed similar results (Figure S1 in supporting information).

3.3 | Low- and high-dose treatment effects for imaging and CSF biomarker outcomes

Figure 2 demonstrates the estimated annual treatment effects before and after dose escalation (see Table S3 in supporting information for more details) for imaging and CSF biomarker outcomes relative to the placebo. Compared to the placebo, gantenerumab produced significant treatment effects in both low and high doses for PiB-PET composite SUVR, CSF Aβ42, and CSF p-tau181; and in high dose only for CSF total tau; and no significant treatment effects in CSF NfL, MRI hippocampus volumes, and MRI precuneus thickness (Figure 2 and more statistical details in Table S3). However, the gantenerumab treatment effect difference between the low dose and the high dose were only

TABLE 2 Clinical/cognitive/biomarker outcomes of participants at baseline and at visits closest to dose escalation

	Baseline[a]			Visit closest to dose escalation[b]		
Outcomes	**Gantenerumab *N* = 52**	**Solanezumab *N* = 50**	**Sharedplacebo *N* = 40**	**Gantenerumab *N* = 47**	**Solanezumab *N* = 37**	**Sharedplacebo *N* = 34**
CDR[c] 0	31 (60)	30 (60)	22 (55)	26 (55)	22 (59)	18 (55)
CDR 0.5	15 (29)	13 (26)	15 (38)	13 (28)	8 (22)	7 (21)
CDR = 1	6 (12)	7 (14)	3 (8)	5 (11)	2 (5)	6 (18)
CDR > 1	0 (0)	0 (0)	0 (0)	3 (6)	5 (14)	2 (6)
N (%)						
Digit Symbol[d]	46.96 ± 20.56	46.06 ± 19.94	46.63 ± 19.12	48.13 ± 23.83	50.69 ± 23.34	54.74 ± 21.64
MMSE[e]	27.10 ± 3.45	26.72 ± 4.11	26.68 ± 3.97	25.91 ± 5.52	26.06 ± 6.45	25.70 ± 6.17
Logical Memory[f]	9.90 ± 6.33	9.86 ± 6.86	9.40 ± 6.45	11.55 ± 7.37	13.38 ± 7.96	12.12 ± 7.59
ISLT[g]	5.96 ± 4.04	6.56 ± 3.95	5.80 ± 4.42	6.13 ± 4.55	5.67 ± 4.26	6.24 ± 4.70
CDR-SB[h]	1.33 ± 2.08	1.37 ± 2.01	1.43 ± 1.87	2.13 ± 3.13	2.61 ± 4.46	2.30 ± 3.39
PiB-PET composite SUVR	2.64 ± 1.23	2.75 ± 1.32	2.62 ± 1.20	2.63 ± 1.25	2.76 ± 1.29	2.58 ± 1.14

Note: Plus-minus values are means ± SD. PiB-PET composite SUVR refers to brain amyloid burden measured by the average SUVR of cortical regions of interest (superior frontal, rostral middle frontal, superior temporal, middle temporal, lateral orbito-frontal, medial orbito-frontal and precuneus), assessed by PiB-PET.

[a]Fifty-two participants were randomized to the solanezumab arm; two did not have post-baseline data and were excluded from the modified intent-to-treat population.

[b]Because the clinical and cognitive assessments were administered annually or every 6 months, the timing of these assessments did not match the starting time of dose escalation, for example, participants started dose escalation in between two visits.

[c]CDR scores range from 0 to 3, with higher scores indicating worse cognition and daily function.

[d]Digit Symbol Substitution Test (Digit Symbol) scores range from 0 to 93, with lower scores indicating poorer cognitive performance.

[e]MMSE scores range from 0 to 30, with lower scores indicating poorer cognitive performance.

[f]Logical Memory Delayed Recall Test (Logical Memory) scores range from 0 to 25, with lower scores indicating poorer cognitive performance.

[g]ISLT scores range from 0 to 12, with lower scores indicating poorer cognitive performance.

[h]CDR-SB scores range from 0 to 18, with higher scores indicating worse cognition and daily function.

Abbreviations: CDR, Clinical Dementia Rating Scale; CDR-SB, Clinical Dementia Rating Sum of Boxes; ISLT, International Shopping List Test-Delayed Recall; MMSE, Mini-Mental State Examination; PiB-PET, positron emission tomography with Pittsburgh compound B; SD, standard deviation; SUVR, standardized uptake value ratio.

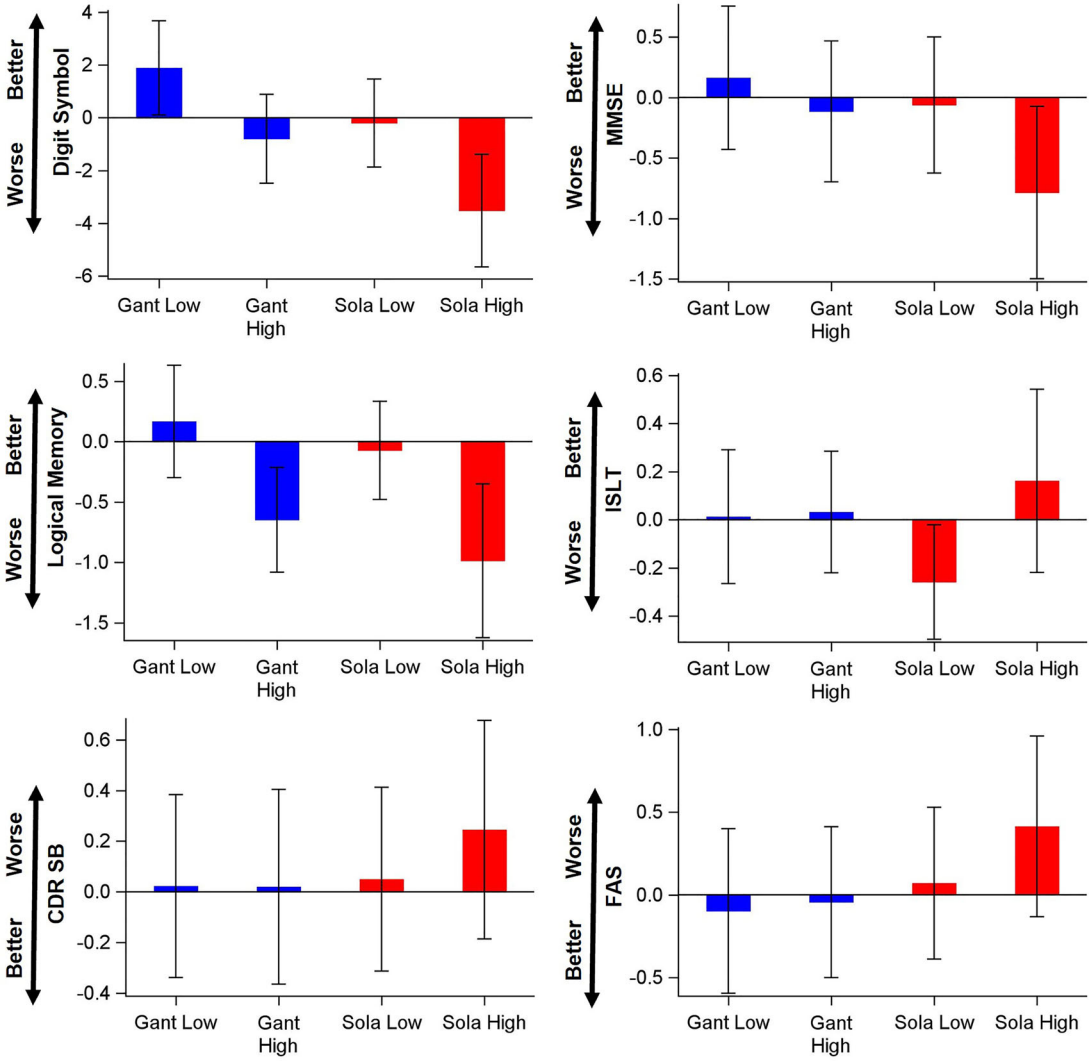

FIGURE 1 Demonstration of the estimated annual low- and high-dose treatment effects and 95% confidence interval (CI) relative to the placebo. A bar with 95% CI covering 0 indicates a non-significant treatment effect for a type I error of 0.05. Better, better than placebo; CDR SB, Clinical Dementia Rating Sum of Boxes; Digit Symbol, Digit Symbol Substitution Test; FAS, Functional Assessment Scale; Gant, gantenerumab; ISLT, International Shopping List Test-Delayed Recall; Logical Memory, Logical Memory Delayed Recall Test; MMSE, Mini-Mental State Examination; Sola, solanezumab; Worse, worse than placebo.

significant in PiB-PET composite SUVR and CSF p-tau181. The gantenerumab high dose reduced the PiB-PET composite SUVR by 0.101 more per year than the lose dose (*P*-value = 0.0095, 95% CI [−0.177, −0.025]), and reduced CSF p-tau181 by 5.20 pg/ml more per year (*P*-value = 0.010, 95% CI [−9.15, −1.25]).

Compared to the placebo, solanezumab produced significant treatment effects in both low and high doses for CSF total Aβ42 (free plus bound Aβ42); no significant treatment effects in PiB-PET composite SUVR, CSF p-tau181, CSF total tau, and MRI precuneus thickness; and significant worsening effects in low dose for CSF NfL and in high dose for MRI hippocampus volumes (Figure 2 and more statistical details in Table S3). The solanezumab high dose did not significantly improve the treatment effect in any imaging or CSF biomarker outcomes compared to the low dose although the increase in CSF total Aβ42 approached significance. The solanezumab high dose increased CSF total Aβ by 115.4 pg/ml more per year than the lose dose (*P*-value = 0.0785. 95% CI [−13.3, 244.1]).

Tables S4 and S5 in supporting information demonstrate the treatment effects for the low dose and the high dose by baseline disease status (asymptomatic vs. symptomatic). Neither treatment showed significant beneficial treatment effect for asymptomatic cohort or symptomatic cohort in clinical and cognitive outcomes. Compared to the placebo, gantenerumab produced similar treatment effects in both low and high doses for PiB-PET composite SUVR for both cohorts, larger treatment effect in high dose for asymptomatic cohort and similar, non-significant treatment effect in both low and high doses for symptomatic cohort for CSF p-tau181 and for CSF total tau; and no treatment effects in CSF NfL, MRI hippocampus volumes, MRI precuneus thickness, and FDG-PET composite SUVR. Compared to the placebo, solanezumab produced significant treatment effect in both

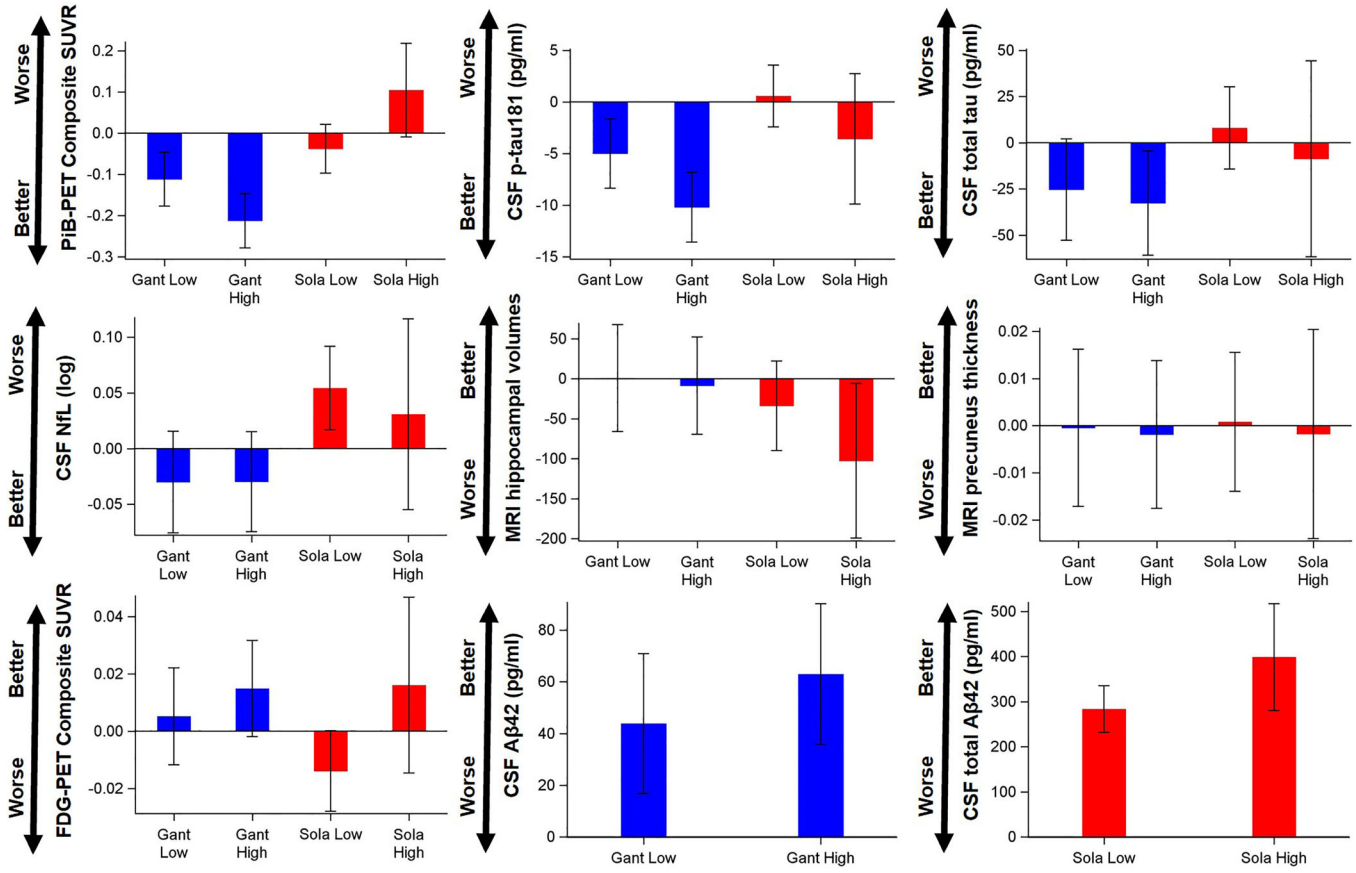

FIGURE 2 Demonstration of the estimated annual low- and high-dose treatment effects and 95% confidence interval (CI) relative to the placebo. A bar with 95% CI covering 0 indicates a non-significant treatment effect for a type I error of 0.05. Better, better than placebo; CSF total Aβ42, cerebrospinal fluid free plus bound amyloid beta 42; FDG-PET, fluorodeoxyglucose positron emission tomography; Gant, gantenerumab; MRI, magnetic resonance imaging; NfL, neurofilament light; PiB-PET SUVR, Pittsburgh compound B positron emission tomography standardized uptake value ratio; p-tau, phosphorylated tau; Sola, solanezumab; Worse, worse than placebo.

low and high doses for both asymptomatic and symptomatic cohorts in CSF total Aβ42 (free + bound Aβ42) and the high dose had larger treatment effect than the low dose in both cohorts; and produced no consistent treatment effects in either cohort for PiB-PET composite SUVR, CSF p-tau181, for CSF total tau, CSF NfL, MRI hippocampus volumes, MRI precuneus thickness, and FDG-PET composite SUVR. Because of the small sample size for each categorical combination (ranging from 8 to 10 for symptomatic high dose to 16 to 24 for asymptomatic low dose) and the larger dropout in the symptomatic group, the estimated treatment effects should be interpreted with caution.

4 | DISCUSSION

The DIAN-TU-001 platform trial successfully and safely implemented drug-specific dose escalation procedures mid-trial based on results from concurrent studies in sporadic AD.[4,5] Results from gantenerumab trials indicated that the 225 mg dose was not fully removing amyloid plaque, and that the dose used had acceptable safety profile to further increase the dose. For solanezumab, the completed phase 3 study indicated a lack of substantial cognitive benefit, while having a safety profile that would allow further increase. To optimize participant safety and characterize the safety profile of the higher doses, participants were carefully monitored during dose escalation, and the schedule of dose escalation and safety assessment was designed to ensure participants' safety. The dose escalation achieved its intended goal for both drugs by demonstrating dose-dependent treatment effects in target engagement (fibrillar Aβ for gantenerumab and soluble Aβ for solanezumab). Compared to the initial dose, the high doses led to larger treatment effects in each drug's Aβ target biomarker (90% more decrease in PiB PET SUVR with high-dose gantenerumab, 41% more increase in CSF total Aβ42 [free + bound] with high-dose solanezumab). The differential treatment effect between low- and high dose was statistically significant for gantenerumab, but not for solanezumab. The lack of significance for solanezumab can be potentially attributed to the shorter duration on high dose (e.g., an average of only 0.8 years before the year-4 biomarker assessment), smaller sample size for high dose due to early dropout, and ceiling effect (e.g., CSF total Aβ42 [free + bound] had been restored to normal or close to normal level during the low-dose treatment period and high dose yielded diminishing treatment effect). Additionally, compared to its

low dose, the gantenerumab high dose also resulted in larger treatment effects in downstream biomarkers such as CSF total tau and CSF p-tau181. Although gantenerumab did not achieve significant treatment effect in the reduction of the annual CSF NfL (log scale) change, the accumulated treatment at year 4 reached significance.[3] This dose-dependent response indicates a possible causal relationship between amyloid reduction and prevention of downstream biomarker progression. However, the augmented high-dose treatment effect demonstrated in biomarkers did not translate into cognitive or clinical outcomes in the double-blind portion of the trial compared to placebo. The slight improvement over placebo in Digit Symbol Substitution Test observed during the gantenerumab low-dose period needs to be interpreted with caution given the relatively small sample size as well as the magnitude of improvement. The faster decline over placebo observed during the solanezumab high-dose period in CDR-SB, MMSE, Digit Symbol Substitution Test, Logical Memory Delayed Recall Test and during the solanezumab low-dose period in ISLT, as noted previously,[16] was contrary to the trend toward clinical and cognitive benefits seen in three large phase III solanezumab trials in sporadic AD,[5,17] and might be attributed to the small sample size and the more severe disease progression around dose escalation compared to placebo (14% participants with CDR > 1 in solanezumab vs. 6% in placebo, Table 2), the drug worsening progression in DIAD, or other unknown factors.

These findings suggest that dose escalation can be implemented during an ongoing phase IIb/III trial when concurrent studies indicated the initial dose may have been insufficient. Although the ideal is to maintain the same dose or to prespecify dose escalation for clinical trials, escalating the dose to achieve greater target engagement[18,19] based on new data is a better alternative than continuation of the trial without any change or restarting the trial due to futility given the logistical and financial burdens to launch a new trial. This is especially critical for clinical trials in rare disease such as the DIAN-TU-001 platform trial with limited enrollment capacity. A potential improvement for future trials with a similar situation is to "re-start the clock" of the follow-up duration at the initiation of dose escalation instead of maintaining the pre-planned overall trial duration. Re-starting the clock increases high-dose drug exposure to amplify the potential treatment effect and ameliorates the exposure difference among participants,[19] which will likely increase the power of the study. However, to maintain similar power levels, additional enrollment would be needed for the increased dose period.

There are some noticeable limitations of the dose escalation procedure. First, variability in individual high-dose durations and participant dropout preceding the administration of high doses will make the evaluation of both the low- and high-dose treatment effects less interpretable. Second, the disease progression of symptomatic participants could diminish the observed treatment effect of the high dose at the group level if the investigational drug is most efficacious at earlier disease stages. Third, the variable low- and high-dose durations limit the types of statistical models that can be used to analyze the treatment effects. For instance, the popular mixed model for repeated measures with the time variable being categorical is less appropriate than the LME model for estimating the treatment effect accurately.

The lack of clinical and cognitive treatment effects in the presence of larger Aβ biomarker target engagement at the higher dose can be attributed to several reasons as explained previously, including but not limited to the lack of clinical and cognitive decline in the asymptomatic cohort, the heterogeneous and short durations of high-dose exposure, the small sample size, and the practice effects of some tests (e.g., Logical Memory Delayed Recall Test) in the asymptomatic group. These are also the overall limitations of the DIAN-TU-001 study. Furthermore, due to the small sample size, the results by disease status (asymptomatic vs. symptomatic) should be interpreted with caution.

5 | COLLABORATORS

5.1 | DIAN-TU Study Team

The DIAN-TU acknowledges the many individuals who have contributed to the DIAN-TU including funding partners, leadership team, core leaders, project arm leaders, study sites, and institutional study partners listed in the following pages.

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CONFLICTS OF INTEREST

Guoqiao Wang, PhD, is the biostatistics core co-leader for the DIAN-TU. He reports serving on a Data Safety Committee for Eli Lilly and Company and as a statistical consultant for Alector. Eric McDade, DO, is the Associate Director of the DIAN-TU. He reports serving on a Data Safety Committee for Eli Lilly and Company and Alector; as a scientific consultant for Eisai and Eli Lilly and Company; receiving institutional grant support from Eli Lilly and Company, F. Hoffmann-La Roche, Ltd., and Janssen. Anne M. Fagan, PhD, is the Biomarker Core Leader of the DIAN-TU. She is a member of the scientific advisory boards for Roche Diagnostics, Genentech, and DiademRes and

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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