The Journal of Prevention of Alzheimer's Disease 13 (2026) 100483

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

The influence of bapineuzumab and semagacestat on rapid progressors: A retrospective cohort study

Kristofer Harris [a], Madison Shyer [a,*], Dulin Wang [b], Elizabeth He [a], Matias Cattani [a], Catherine Zhang [a], Christine M. Farrell [a], Xiaoqian Jiang [b], Yejin Kim [b], Paul E. Schulz [a]

[a] Department of Neurology, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA
[b] McWilliams School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, TX, USA

ARTICLE INFO

Keywords:
Rapid Progressor
Semagacestat
Bapineuzumab
CATE
Cohort

ABSTRACT

Background: A subset of Alzheimer's disease patients progresses much more rapidly than average. These rapid progressors exhibit accelerated cognitive and functional decline. Potential differences in Alzheimer's biomarkers for rapid progressors and their responses to disease-modifying treatments remain poorly understood, with previous clinical trials and studies producing limited biomarker data and inconsistent results.
Objectives: Examine differences in rapid progressor versus non-rapid progressor outcomes in two AD treatment trials (bapineuzumab and semagacestat) and investigate cognitive and biomarker progression in the placebo groups.
Design: Retrospective cohort study.
Setting: Four randomized, double-blind, phase 3 clinical trials from the Center for Global Clinical Research Data (Semagacestat) and the Yale University Open Data Access Project (Bapineuzumab).
Participants: 4,902 patients (2,355 in bapineuzumab trials, 2,647 in semagacestat trials). Rapid progressors were operationally defined as the 10% of patients with the largest changes in cognitive scores from baseline to trial end.
Intervention: Bapineuzumab (monoclonal antibody) and Semagacestat (γ-secretase inhibitor).
Measurements: Cognitive assessments (CDR-SB, MMSE, ADAS-Cog, ADCS-ADL) and biological markers (CSF and plasma levels, MRI, FDG PET Scan, and Amyloid PET Scan) at baseline and endpoint.
Results: Rapid progressors showed distinct baseline characteristics in both the bapineuzumab and semagacestat trials: younger age (61.27 vs 63.14 years, $p=0.008$; and, 72.64 v. 73.64 years, $p=0.046$), a higher proportion of APOE4 carriers (87.6% vs 41.4%, $p<0.001$; and, 85.2% vs 49.3%, $p = 0.022$), and greater cognitive impairment across all measures ($p<0.001$). Both progression groups demonstrated improvement in specific biomarkers with treatment, though with different patterns. With bapineuzumab according to Conditional Average Treatment Effect analysis, rapid progressors showed biomarker improvement in amyloid CSF, p-Tau CSF, and amyloid PET scan, while non-rapid progressors demonstrated biomarker improvements in p-Tau CSF, amyloid PET, and MRI. With semagacestat, rapid progressors showed improvements in amyloid CSF and plasma while non-rapid progressors showed improvements in amyloid CSF, FDG PET, and MRI.
Conclusions: This study provides crucial insights for clinical practice and trial design. The distinct response patterns between progression groups suggest that early identification and balancing of RPs between groups could improve clinical trial efficiency. The findings support the development of personalized treatment approaches for rapid progressors, who have aggressive disease progression. These results may significantly modify clinical trial design and patient care in Alzheimer's disease.

1. Introduction

Rapid progressors (RPs) in Alzheimer's disease (AD) are individuals who exhibit an accelerated decline in cognitive and functional abilities compared to the expected trajectory of disease progression [1–4]. It is unknown whether RPs are responsive, either via cognitive assessments

* Corresponding author at: 1941 East Rd, Houston, TX 77054, USA
E-mail address: Madison.Shyer@uth.tmc.edu (M. Shyer).

https://doi.org/10.1016/j.tjpad.2026.100483
Received 23 July 2025; Received in revised form 1 December 2025; Accepted 7 January 2026
Available online 21 January 2026

or biomarkers, to drugs designed to slow the progression of the disease both in clinical trials or commercially-available treatments.

One intervention that has investigated RPs —aducanumab, an anti-amyloid beta (Aβ) monoclonal antibody— has also been at the center of extensive debate regarding its efficacy and approval process [5]. A critical issue in its clinical trials has been that the ENGAGE study had a higher number of RPs in the high dose group versus EMERGE (9 patients in ENGAGE and 5 in EMERGE). Excluding these RPs changed the Clinical Dementia Rating - Sum of Boxes (CDR-SB) outcome, improving the score change in the high-dose ENGAGE group. The analysis of this trial with regard to RPs (as defined by CDR-SB) did not include how biomarker outcomes were affected. Given the recent updates to the biomarker classification system [6], which helps to define AD biologically, a more robust understanding of the biology of RPs and its potential effects on treatments is necessary.

Many other anti-Aβ medications have been investigated. Bapineuzumab and semagacestat both underwent phase 3 clinical trials for the treatment of AD [7,8]. Bapineuzumab is a monoclonal antibody whose mechanism of action is similar to aducanumab's, i.e. binding to and clearing beta amyloid deposits in the brain cortex. Semagacestat is a γ-secretase inhibitor that lowers the production of Aβ in the blood, spinal fluid, and brain. Unfortunately, bapineuzumab was not associated with significant improvement in clinical outcomes, i.e., it did not slow disease progression. Additionally, higher doses of Semagacestat were correlated with a decline in functional ability and an increase in adverse events, resulting in early termination of the clinical trial. Patients in the trial were followed for 7 months afterwards to collect safety data. Neither the bapineuzumab nor the semagacestat studies investigated the effects of these medications in RPs; therefore, it is not known whether the medications have any effect on RP versus NRP biomarkers.

The objectives for this study were to determine whether treatment with semagacestat or bapineuzumab affected 1) the biomarker outcomes for RPs versus NRPs or 2) the relationship between cognitive test progression and endpoint biomarker outcomes (plasma, CSF, MRI, PET) of RPs versus NRPs over the course of the clinical trials. We hypothesized that semagacestat and bapineuzumab would have different effects on RP and NRP biomarker outcomes and that in the placebo group, RPs would have greater decline versus NRPs on cognitive testing and the rate of biomarker change from baseline to the patients' final visit.

2. Methods

2.1. Data Source

We analyzed data from four randomized clinical trials (RCTs) from the Yale University Open Data Access Project (YODA) and Center for Global Clinical Research Data (Vivli) [9–12]. Two RCTs were multicenter, double-blind, phase 3 studies of bapineuzumab in patients with mild to moderate AD with and without APOE4 (NCT00574132 & NCT00575055). The other two RCTs were multicenter, double-blind, phase 3 trials studies of semagacestat in patients with mild AD (NCT00594568 & NCT00762411). The RCT datasets for semagacestat were combined, as were the datasets for bapineuzumab. eTable 1 demonstrates the clinical trial details, eTable 2 illustrates the schedule of events for each of the RCTs, and Fig. 1 shows the overall analysis flowchart.

2.2. Patients and Treatments

Randomized patients, including those who discontinued from the clinical trial early, were included in our analysis. One semagacestat RCT tested 140 mg and 100 mg doses versus placebo, and the other tested only the 140 mg dose versus placebo. For our analysis, patients who received either dose of semagacestat were combined into a treatment group. The bapineuzumab RCTs studied 0.5 mg/kg and 1 mg/kg dosages, which for our purposes were combined into one treatment group.

2.3. Rapid Progressor Definitions

For these analyses, we used our previously described RP definitions

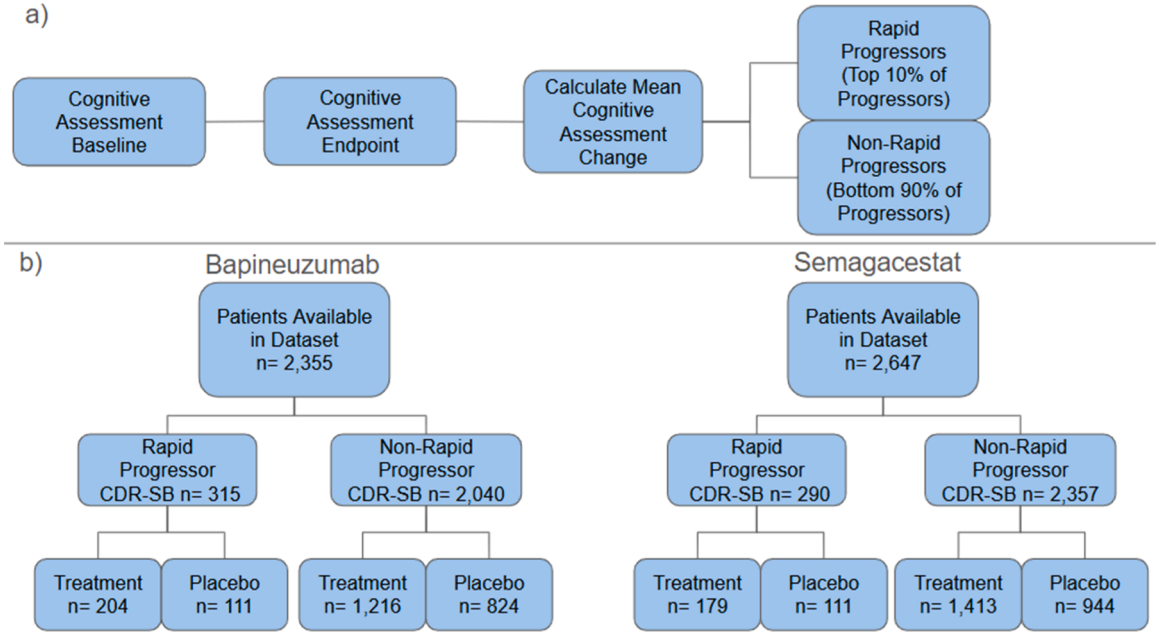

Fig. 1. Rapid Progressor Designation Methodology and Analyses Overview Flowchart.
a) Description of how the mean cognitive assessment change is calculated. The top 10% of patients who progress on the cognitive tests (CDR-Sum of Boxes (CDR-SB), Mini-Mental Status Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Alzheimer's Disease Cooperative Study- Activities of Daily Living (ADCS-ADL)) are classified as rapid progressors (RP), and the bottom 90% of patients are considered non-rapid progressors (NRP). b) Overview flowchart for the bapineuzumab and semagacestat analyses. The main analysis, which identifies RPs/NRPs based on the CDR-SB assessment, is represented in the flowchart. In all of the original clinical trials for bapineuzumab and semagacestat, 60% of patients were randomized to the treatment arms.

(Ma & Shyer, 2024). We have defined RPs as the 10% of patients with the greatest changes in cognitive scores from baseline to trial's end (Fig. 1). In this study, if a patient discontinued a trial prior to study completion, then we used the change in score from baseline to the last cognitive test scores recorded. Cognitive tests included the 1) CDR-SB (0–18, higher scores indicating greater functional impairment), 2) Mini Mental State Examination (MMSE) (0–30, lower scores indicating greater cognitive impairment), 3) Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (0–90, higher scores indicating greater cognitive impairment), and 4) Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) (0–78, lower scores indicating greater functional impairment). The bapineuzumab RCTs utilized the CDR-SB, MMSE, and ADAS-Cog, and the semagacestat RCTs utilized all cognitive assessments.

Patients with a change of more than 22 for ADAS-Cog, 24 for the ADCS-ADL, 6 for CDR-SB, and 10 for MMSE met our definition of RP, i.e., the 10% of patients with the greatest changes in cognitive scores. Since the CDR-SB was a primary outcome for the aducanumab trial and lecanemab trials, was a secondary outcome measure in the donanemab trial, and is an FDA recognized measure of decline, we used the CDR-SB RP definition in this study. However, in the supplement we show the same analyses using the other cognitive test RP definitions.

2.4. Outcomes

Biomarker outcomes such as plasma, CSF, MRI, and PET scan variables were included in the analysis, as available. For the semagacestat analyses, we included CSF Aβ 42/40 ratio, CSFAβ 42, CSF Aβ 40, plasma Aβ 42/40 ratio, plasma Aβ 42, plasma Aβ 40, Entorhinal Cortex Volume, Hippocampal Volume, Whole Brain Volume, Ventricular Volume, and FDG PET scan SUVR. For the bapineuzumab analyses, we included CSF Aβ 42/40 ratio, CSF Aβ 42, CSF Aβ 40, CSF p-Tau, Hippocampal Volume, Whole Brain Volume, Ventricular Volume, and Amyloid PET scan SUVR.

2.5. Statistical Analysis

For demographic variables, mean (standard deviation) and frequency (percentage), and the corresponding p-value (chi-square, *t*-test) were calculated. For non-demographic variables, the mean difference between the endpoint value and the baseline values were computed. Missing data was addressed using imputation procedures in all analyses.

2.6. Conditional Average Treatment Effect (CATE) Analysis

We observed a significant difference between RP and NRP in clinical

Table 1
Bapineuzumab and Semagacestat Demographic and Cognitive Assessment Findings for Rapid Progressors and Non-Rapid Progressors based on the CDR-SB Rapid Progressor Definition.

		BAPINEUZUMAB RP (N=315), NRP (N=2,040)				SEMAGACESTAT RP (N=290), NRP (N=2,357)			
	RP or NRP	**Baseline**	**p-value**	**Overall Endpoint Mean Change**	**p-value**	**Baseline**	**p-value**	**Overall Endpoint Mean Change**	**p-value**
Age	RP	69.57 (8.24)	0.008			72.64 (8.42)	0.04		
	NRP	70.75 (9.22))				73.64 (8.04)			
Male	RP	131 (41.6%)	<0.001			123 (42.4%)	0.46		
	NRP	953 (46.7%)				1058 (44.9%)			
Caucasian	RP	300 (95.2%)	0.665			247 (85.2%)	<0.001		
	NRP	1927 (94.5%)				1750 (74.2%)			
Hispanic	RP	5 (1.6)	0.082						
	NRP	75 (3.7)							
APOE4 Carrier	RP	276 (87.6%)	<0.001			164 (56.6%)	0.02		
	NRP	845 (41.4%)				1161 (49.3%)			
CDR-SB	RP	5.82 (2.38)	<0.001	6.81 (1.90)	<0.001	5.73 (2.17)	0.57	7.59 (1.99)	<0.001
	NRP	5.11 (2.87)		0.8 (1.64)		5.63 (2.91)		1.07 (1.79)	
ADAS-Cog	RP	28.66 (8.63)	<0.001	14.29 (9.24)	<0.001	40.58 (11.02)	<0.001	20.31 (13.70)	<0.001
	NRP	21.97 (9.48)		3.20 (6.97)		34.63 (11.12)		4.76 (9.55)	
MMSE	RP	19.17 (2.65)	<0.001	-7.93 (4.82)	<0.001	19.6 (2.75)	<0.001	-7.77 (5.00)	<0.001
	NRP	21.25 (3.20)		-2.02 (4.18)		20.82 (3.14)		-1.85 (3.72)	
ADCS-ADL						2.44 (1.41)	0.01	-1.45 (1.40)	<0.001
						2.67 (1.46)		-0.47 (1.26)	

Continuous variables are presented as mean and standard deviation, and categorical variables as frequency and percentage. When comparing rapid progressors and non-rapid progressors, or mean endpoint values, variables that demonstrated the same mean outcome at 2 decimal places were extended to 4 decimal places (0.02 vs 0.0254). ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study- Activities of Daily Living; APOE: Apolipoprotein E; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MMSE: Mini-Mental Status Examination; NRP: Non-Rapid Progressor; RP: Rapid Progressor.

and biological variables at baseline (Tables 1-2). These differences suggest that treatment effects may not be uniform across the population and the group-level comparison might reflect those imbalances. To account for such heterogeneity, we estimated individualized Conditional Average Treatment Effects (CATE) using a causal forest model. Causal forests are an extension of random forests designed to estimate treatment effect heterogeneity under the potential outcome's framework [13]. Previously, we leveraged causal forest for heterogeneity estimation to identify moderators affecting treatment effect [14]. Building on this, we identified individualized CATEs using various biological outcome measures and quantified the RP and NRP group CATE in a post-hoc manner. By conditioning on a rich set of baseline features, causal forests aim to adjust for such heterogeneity and uncover subgroups with differential treatment responses.

2.7. Additional Analyses on Amyloid Status and Disease Severity

Two additional analyses were conducted in order to understand whether baseline characteristics that are usually used in contemporary clinical trials influenced outcomes. First, to assess the impact of amyloid status on bapineuzumab results, we included only patients with a PIB PET scan SUVR $\geq$ 1.35. We compared RPs and NRPs in regards to the PIB PET scan values at the baseline, overall endpoint, and the endpoint mean change for both the treatment and placebo groups. Second, to examine the influence of disease severity on bapineuzumab and semagacestat outcomes, we restricted the sample to include only patients with a baseline MMSE of $\geq$ 20, which has commonly been done in more recent clinical trials. As in the amyloid analysis, we compared RPs and NRPs. However, this analysis also included MMSE at baseline, PIB PET Scan, CSF Aβ 42/40, and plasma Aβ 42/40 as outcomes.

2.8. Ethical approval

The UTHealth at Houston Institutional Review Board and the Committee for the Protection of Human Subjects (CPHS) reviewed the study and classified it as "non-human subjects research" due to the use of de-identified retrospective data. The study was approved with a waiver of HIPAA authorization and informed consent waiver.

3. Results

3.1. Bapineuzumab

The bapineuzumab analyses included 2,355 patients (eTable 3), of whom 315 met our definition for CDR-SB RPs and 2,040 were CDR-SB NRPs. Of the RPs, 204 (64%) received treatment and 111 (35%) received placebo. Of the NRPs, 1,216 (59%) received treatment and 824 (40%) received placebo. The proportion of RPs and NRPs receiving treatment was similar to the randomization ratios found in the original clinical trials in which 60% of patients were randomized into the treatment arms. The CDR-SB RP baseline characteristics and measurements, endpoint effects, and CATE values are shown in Tables 1 and 2.

In the bapineuzumab RP CDR-SB analysis, the mean age was 61.27 (SD: 10.01) for RPs and 63.14 (SD: 11.92) for NRPs (p-value: 0.008). Males were 49.2% of RPs, and 77.4% NRPs (<0.001). Caucasians were 95.2% of RPs and 94.5% of NRPs. APOE4 carriers were 87.6% of the RPs and 41.4% of the NRPs (p-value: <0.001).

At baseline, RPs were more cognitively impaired versus NRPs on the CDR-SB, ADAS-Cog, and MMSE (p-values: <0.001). RPs were also more likely to have worse biomarker profiles than NRPs on CSF Aβ 42/40, Aβ PET scans, CSF p-Tau, volumes of the left/right hippocampi, whole brain, and ventricles, (p-values: <0.001).

At the endpoints, no improvements were noted on biomarkers with bapineuzumab treatment for the CDR-SB RP definition analysis. However, based on the CATE analysis, RPs showed improvements with CSF Aβ 40, CSF p-Tau, and amyloid PET scans. On CATE analyses, NRPs had improvements in CSF Aβ 42/40, CSF Aβ 42, CSF Aβ 40, CSF p-Tau, hippocampal volume, ventricular volume, and amyloid burden on PET scans.

There were no biomarkers in RPs that showed improvement with bapineuzumab treatment identified through both the endpoint treatment effect and CATE analyses; however, NRPs demonstrated improvement in amyloid PET and CSF p-Tau.

3.2. Semagacestat

The semagacestat analysis had 2,647 patients, of whom 290 met our definition for CDR-SB RPs, and 2,357 as CDR-SB NRPs. Of the RPs, 179 (61%) received treatment and 111 (38%) received placebo. Of the NRPs, 1,413 (57%) received treatment and 944 (40%) received placebo. Again, the proportion of RPs and NRPs receiving treatment was similar to the randomization ratios found in the original clinical trials in which 60% of patients were randomized into the treatment arms. The semagacestat RP CDR-SB analysis had a mean age of 72.64 (SD: 8.42) for RPs and 73.64 (SD: 8.04) for NRPs (p-value: 0.046). Males represented 42.4% of RPs, and 44.9% NRPs (p-value: 0.461). Caucasians constituted 85.2% of RPs and 74.2% of NRPs (p-value: <0.001). APOE4 carriers represented 85.2% of the RPs and 49.3% of the NRPs (p-value: 0.022). Again, RPs were more likely to be cognitively progressed at baseline when using the ADAS-Cog (p-values: <0.001), MMSE (p-values: <0.001), and ADCS-ADL (p-values: 0.01) assessments.

At baseline, RPs were more likely to have worse biomarker profiles than NRPs, including CSF Aβ42/40 (p-value: 0.004), hippocampal volumes (p-values: <0.001), whole brain volume (p-value: <0.001), and ventricular volume (p-value: <0.001).

At the endpoint, only plasma Aβ 42/40 improved significantly for RPs (p-value: 0.01) and CSF Aβ 40 for NRPs (p-value: 0.02). Based on the CATE analysis, however, RPs showed improvement in CSF Aβ 42/40, CSF Aβ 40, plasma Aβ 42/40, and plasma Aβ 42. NRPs had improvements in CSF Aβ 40, plasma Aβ 42/40, plasma Aβ 40 Plasma, and FDG PET. The only biomarkers that showed improvement with treatment identified through both the endpoint treatment effect and CATE analyses for RPs was plasma Aβ 42/40 and CSF Aβ 40 for NRPs.

The baseline, endpoint, and CATE tables for the other RP definitions (ADAS-Cog, MMSE, and ADCS-ADL) is found in eTables 4–9. An overview and analysis of the trends for biomarkers that demonstrated beneficial treatment effects is in eTable 10. Altogether, when comparing the frequency of biomarkers that showed benefit from treatment, NRPs clearly had more positive outcomes than RPs (eTable 10).

3.3. Cognitive and Biomarker Progression in the Placebo Group(s)

For our second objective - examine cognitive and biomarker progression in placebo arms of both drug trials—Tables 2 and 3, and eTables 4–9—demonstrate that RPs are more progressed at baseline than NRPs, as noted above. Fig. 2 illustrates the cognitive test score progression for the placebo group RPs and NRPs throughout the clinical trials. Overall, RPs were more progressed at baseline, then continued to decline throughout the clinical trial at a consistent rate when compared with NRPs who progressed at a much slower rate.

3.4. Amyloid Status and Disease Severity

After restricting the bapineuzumab analyses to patients with a PIB PET scan SUVR $\geq$ 1.35, RPs showed more advanced disease via PIB PET scan at baseline than NRPs (eTable 11). Within this sample, RPs receiving treatment had significantly higher Aβ levels than those in in the placebo group.

When restricting to patients with an MMSE score of $\geq$ 20, RPs demonstrated worse baseline characteristics for MMSE scores, PIB PET scan, and CSF Aβ 42/40 in the bapineuzumab portion of the analysis (eTable 12), consistent with the original analysis (Table 2). The NRPs

Table 2
Bapineuzumab and Semagacestat Baseline, Endpoint, and Conditional Average Treatment Effect Analysis of Rapid Progressors and Non-Rapid Progressors based on the CDR-SB Rapid Progressor Definition.

		Baseline	p-value	Overall Endpoint Mean Change	p-value	Endpoint Mean Change Treatment	Endpoint Mean Change Placebo	p-value	Treatment Beneficial via Endpoints?	CATE	Treatment Beneficial via CATE?
BAPINEUZUMAB RP (N=315), NRP (N=2,040)											
Aβ 42/40 CSF	RP	0.083 (0.0165)	<0.001	0.0056 (0.0113)	<0.001	0.0048 (0.0117)	0.007 (0.0107)	0.09	No	-0.00027	No
	NRP	0.0907 (0.0236)		0.0009 (0.0094)		0.001 (0.0072)	0.0005 (0.0119)	0.22	No	0.00042	Yes
Aβ 42 CSF	RP	510.31 (143.02)	<0.001	-32.36 (78.36)	<0.001	-35.13 (73.93)	-27.26 (86.01)	0.41	No	-22.68	No
	NRP	563.05 (177.79)		1.39 (55.67)		2.49 (52.93)	-0.22 (59.45)	0.29	No	4.05	Yes
Aβ 40 CSF	RP	6,258.64 (1,646.00)	0.065	-621.97 (1,100.09)	<0.001	-612.2 (1192.78)	-639.91 (910.21)	0.81	No	-194.31	Yes
	NRP	6,436.01 (1,580.60)		-68.46 (657.88)		-75.42 (578.71)	-58.17 (760.06)	0.58	No	-3.76	Yes
p-Tau CSF	RP	108.61 (32.28)	<0.001	-6.58 (11.11)	<0.001	-6.94 (10.9)	-5.9 (11.5)	0.43	No	-3.57	Yes
	NRP	99.74 (29.17)		-0.21 (5.28)		-0.36 (5.3)	0.02 (5.23)	0.1	No	-0.08	Yes
Left Hippocampal Volume	RP	2.1123 (0.2724)	<0.001	-0.0899 (0.0379)	<0.001	-0.0902 (0.0379)	-0.0891 (0.0379)	0.79	No	-0.00745	No
	NRP	2.2935 (0.3028)		-0.0648 (0.0351)		-0.0649 (0.0358)	-0.0647 (0.0341)	0.9	No	0.00029	Yes
Right Hippocampal Volume	RP	2.2343 (0.2877)	<0.001	-0.0768 (0.0490)	<0.001	-0.0769 (0.0459)	-0.0767 (0.0543)	0.97	No	-0.00417	No
	NRP	2.3691 (0.3092)		-0.0629 (0.0392)		-0.0624 (0.0386)	-0.0636 (0.0401)	0.51	No	0.0013	Yes
Whole Brain Volume	RP	1,003.48 (75.32)	<0.001	-30.29 (12.99)	<0.001	-29.91 (13.15)	-30.99 (12.72)	0.47	No	-2.42	No
	NRP	1,025.99 (74.01)		-17.35 (10.69)		-17.74 (10.67)	-16.76 (10.68)	0.04	No	-0.76	No
Ventricular Volume	RP	52.52 (17.08)	<0.001	11.01 (4.96)	<0.001	10.92 (4.84)	11.18 (5.19)	0.65	No	1.99	No
	NRP	48.76 (15.54)		5.29 (2.70)		5.36 (2.77)	5.18 (2.58)	0.13	No	-0.06	Yes
Amyloid (PIB) PET SUVR	RP	1.9033 (0.1759)	<0.001	-0.0081 (0.0694)	<0.001	-0.0131 (0.0677)	0.0012 (0.0718)	0.08	No	-0.02008	Yes
	NRP	1.7610 (0.2378)		0.0056 (0.0574)		0.0036 (0.0584)	0.0085 (0.0557)	0.054	No	-0.00342	Yes
SEMAGACESTAT RP (N=290), NRP (N=2,357)											
Aβ42/40 CSF	RP	0.0876 (0.0121)	0.004	0.0014 (0.0028)	<0.001	0.0013 (0.0026)	0.0015 (0.0032)	0.61	No	0.000196	Yes
	NRP	0.085 (0.0143)		0.0008 (0.0026)		0.0009 (0.0027)	0.0007 (0.0025)	0.07	No	-0.000207	No
Aβ 42 CSF	RP	1,006.38 (141.42)	0.37	0.02 (41.52)	0.16	-1.48 (45.2)	2.44 (34.82)	0.4	No	-1.21	No
	NRP	997.31 (165.24)		-4.18 (48.88)		-4.65 (46.61)	-3.46 (52.1)	0.56	No	-4.08	No
Aβ 40 CSF	RP	11,708.17 (1,497.27)	<0.001	-270.56 (536.71)	0.04	-274.85 (549.34)	-263.63 (518.05)	0.86	No	-49.37	Yes
	NRP	12,108.73 (1,461.38)		-203.86 (543.19)		-223.85 (577.07)	-173.93 (486.87)	0.02	Yes	-17.98	Yes
Aβ 42/40 Plasma	RP	0.2304 (0.1188)	0.84	-0.0067 (0.15)	0.44	0.012 (0.0885)	-0.0369 (0.2067)	0.01	Yes	0.0115	Yes
	NRP	0.2315 (0.0802)		0.0042 (0.24)		0.0084 (0.2987)	-0.0021 (0.0863)	0.2	No	0.0478	Yes
Aβ 42 Plasma	RP	38.15 (10.18)	0.81	5.26 (14.60)	0.72	5.15 (13.42)	5.43 (16.38)	0.87	No	0.44	Yes
	NRP	38.31 (11.20)		4.96 (13.42)		5.12 (13.77)	4.71 (12.87)	0.46	No	-0.05	No
Aβ 40 Plasma	RP	175.3 (45.95)	0.56	30.04 (72.11)	0.30	25.42 (70.88)	37.5 (73.74)	0.17	No	2.9	No
	NRP	173.58 (48.61)		25.54 (71.16)		26.7 (71.88)	23.78 (70.06)	0.32	No	-10.93	Yes
Left Entorhinal Cortex Volume	RP	472.45 (48.45)	0.34	-17.66 (11.98)	<0.001	-18.45 (12.76)	-16.37 (10.52)	0.13	No	-0.47	No
	NRP	476.03 (62.18)		-10.89 (9.99)		-11.08 (10.51)	-10.61 (9.15)	0.25	No	-2.33	No

(*continued on next page*)

Table 2 (*continued*)

		Baseline	p-value	Overall Endpoint Mean Change	p-value	Endpoint Mean Change Treatment	Endpoint Mean Change Placebo	p-value	Treatment Beneficial via Endpoints?	CATE	Treatment Beneficial via CATE?
Right Entorhinal Cortex Volume	RP	452.78 (55.60)	0.24	-16.58 (11.60)	<0.001	-17.06 (12.87)	-15.8 (9.19)	0.33	No	-0.79	No
	NRP	448.13 (65.82)		-9.11 (8.98)		-9.42 (9.74)	-8.64 (7.66)	0.03	No	-1.53	No
Left Hippocampal Volume	RP	1,688.91 (186.25)	<0.001	-70.89 (47.41)	<0.001	-74.29 (52.35)	-65.38 (37.69)	0.09	No	-2.02	No
	NRP	1,743.78 (206.06)		-39.78 (37.84)		-40.53 (39.48)	-38.64 (35.22)	0.22	No	-10.68	No
Right Hippocampal Volume	RP	1,742.43 (174.05)	<0.001	-68.37 (47.96)	<0.001	-69.91 (47.61)	-65.86 (48.61)	0.48	No	-5.3	No
	NRP	1,792.57 (190.11)		-40.88 (39.39)		-42.93 (41.76)	-37.79 (35.33)	0.001	No	-4.62	No
Whole Brain Volume	RP	1,005.84 (47.02)	<0.001	-10.57 (8.00)	<0.001	-10.68 (7.81)	-10.38 (8.32)	0.76	No	-0.24	No
	NRP	1,024.76 (59.38)		-6.00 (6.28)		-6.09 (6.68)	-5.85 (5.61)	0.34	No	-0.47	No
Ventricular Volume	RP	55.88 (11.38)	<0.001	5.27 (3.54)	<0.001	5.26 (3.04)	5.25 (4.23)	0.98	No	0.14	No
	NRP	51.87 (12.13)		2.37 (2.33)		2.43 (2.48)	2.28 (2.08)	0.12	No	0.11	No
FDG PET SUVR	RP	1.4334 (0.0627)	0.22	0.0166 (0.06)	<0.001	0.0216 (0.0561)	0.0085 (0.0684)	0.09	No	-0.00179	No
	NRP	1.4264 (0.0970)		0.0033 (0.06)		0.0026 (0.0653)	0.0042 (0.0445)	0.48	No	0.0134	Yes

Continuous variables are presented as mean and standard deviation, and categorical variables as frequency and percentage. When comparing rapid progressors and non-rapid progressors, or mean endpoint values, variables that demonstrated the same mean outcome at 2 decimal places were extended to 4 decimal places (0.02 vs 0.0254). For Aβ 42/40, Aβ 42, Entorhinal Cortex Volume, Hippocampal Volume, Whole Brain Volume, and FDG PET SUVR a positive CATE value indicates treatment benefit. For Aβ 40, Ventricular Volume, and p-Tau a negative CATE value indicates treatment benefit. For the "Treatment Beneficial via Endpoints?" column, the treatment was only considered beneficial if it was both statistically significant and the treatment group had a better outcome than the placebo group for the specific measure. ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study- Activities of Daily Living; Aβ: Amyloid beta; APOE: Apolipoprotein E; CSF: Cerebrospinal Fluid; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CATE: Conditional Average Treatment Effect; FDG: Fluorodeoxyglucose; MMSE: Mini-Mental Status Examination; NRP: Non-Rapid Progressor; PET: Positron Emission Tomography; PIB: Pittsburgh Compound B; RP: Rapid Progressor; SUVR: Standardized uptake value ratio.

demonstrated a statistically significant increase in CSF Aβ 42/40, indicating a positive response to treatment. For the semagacestat analysis portion of the analysis, RPs were significantly more impaired at baseline on the MMSE, but not for plasma Aβ 42/40 or CSF Aβ 42/40. Unlike in the original analysis (Table 2), the endpoint mean change in plasma Aβ 42/40 was no longer statistically significant for the RPs when comparing treatment with placebo. This indicates that once the MMSE falls below 20, RP patients have an elevated amount of plasma Aβ 42/40.

4. Discussion

In this cohort study, we determined that there were significant differences between RPs and NRPs in regard to baseline characteristics, biological endpoint values, and CATE. RPs are more likely to be young, more cognitively progressed at baseline, female (for bapineuzumab), have an ApoE 4 allele, and have worse biomarker profiles. Throughout the clinical trials, by definition, they progressed much more rapidly than the NRPs. While both RPs and NRPs responded to the treatments (bapineuzumab and semagacestat), they did so in different ways, and NRPs had greater responses to treatments.

4.1. Baseline Differences and Timing of Rapid Progressors Identification

Similar to another study [15], we found that RPs are more progressed at baseline as measured by cognitive tests. The differences on the ADAS-Cog, for example, were nearly 7 points and were 1 to 2 points for the MMSE. It is unclear whether this small effect size is clinically significant at baseline. However, the RPs decline quickly throughout the clinical trial (Fig. 2), such that the cognitive differences at trial conclusion are likely to be very clinically significant. Baseline differences in ADLs, in contrast, were minimal. This could be because one would not have meet the enrollment criteria for being early in the course of AD if they were more impaired. Furthermore, we have included a figure in the supplementary (eFigure 1) displaying the number of RPs identified by each individual/combination of tests (non-overlapping) for ease of interpretation.

Biomarkers also differed between groups, with RPs having more atrophy on MRI, more Aβ deposition, and higher levels of p-Tau in the CSF. In comparing the progression rates between RPs and NRPs during the clinical trial, Fig. 2 shows that RPs experienced a significantly faster rate of decline compared to NRPs.

Sex differences in AD progression are known, with studies showing that women experience cognitive decline at approximately twice the rate of men [16,17]. Additionally, women with AD pathology are more likely to exhibit clinical symptoms of the disease than men. In our study, the RP group included a statistically significant higher proportion of women. In addition to other factors such as age and APOE status, which also differed significantly between RPs and NRPs, sex may have an important role in RP development and should be considered in future studies.

Identification of RPs within the first few clinic visits could be very beneficial to both the patient and caregivers so they can take this information into account when making life and treatment decisions. In addition, it would be valuable to identify RPs early for clinical trials so the number of RPs in the treatment and placebo groups could be balanced, avoiding the concerns of the aducanumab trial. We previously published a model to predict RPs within a clinical trial setting that uses data up until week 28 (6 months) [1]. Ideally this could occur during the clinical evaluation and before entering a study so that it could be taken into account for randomization. It is therefore possible to create and use a similar model in the clinic setting to help clinicians predict who will become an RP and personalize care accordingly.

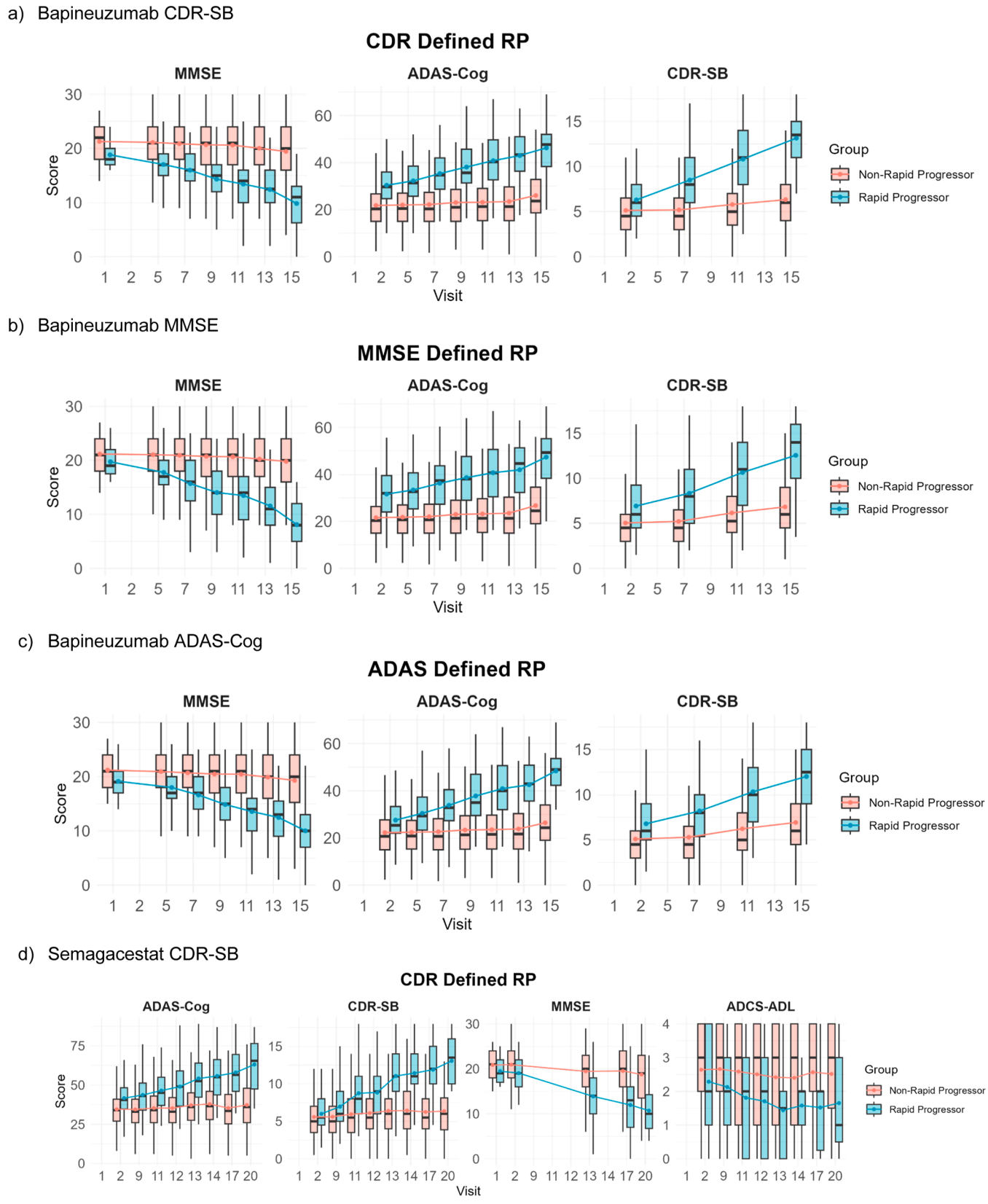

Fig. 2. Longitudinal Cognitive Test Scores by Visit for Rapid Progressors and Non-Rapid Progressors.
Cognitive assessment means and standard deviations at visits in which the test is conducted. For bapineuzumab, the CDR-SB, MMSE, ADAS-Cog assessments are shown, and for semagacestat the CDR-SB, MMSE, ADAS-Cog, ADCS-ADL assessments are shown based on the rapid progressor definition. a) Bapineuzumab CDR-SB; b) Bapineuzumab MMSE; c) Bapineuzumab ADAS-Cog; d) Semagacestat CDR-SB; e) Semagacestat MMSE; f) Semagacestat ADAS-Cog; and g) Semagacestat ADCS-ADL. ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study- Activities of Daily Living; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MMSE: Mini-Mental Status Examination; NRP: Non-Rapid Progressor; RP: Rapid Progressor. Higher scores represent worse cognitive function on the ADAS-Cog and the CDR-SB. Lower scores represent worse function for the MMSE and ADCS-ADL.

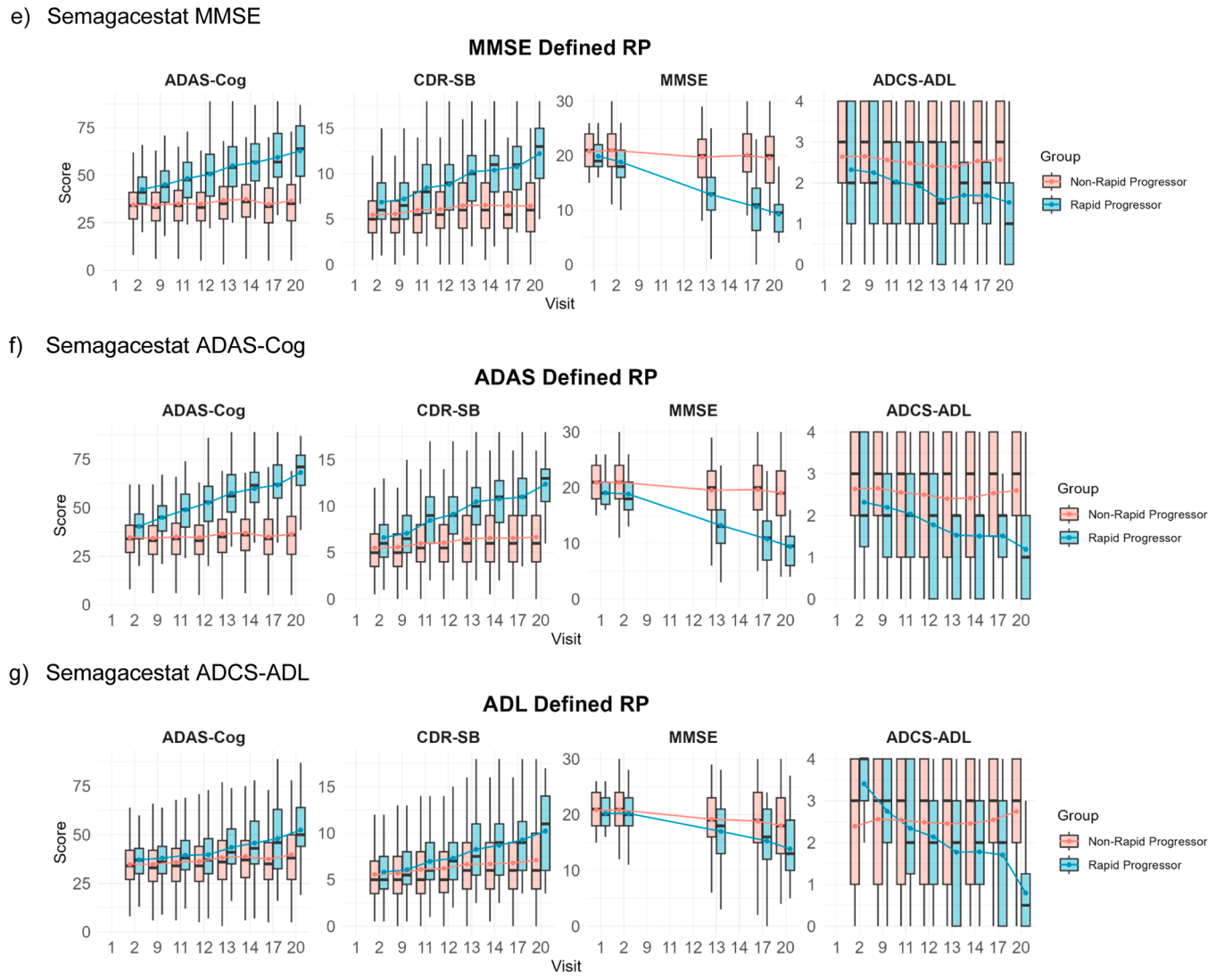

Fig. 2. (*continued*).

4.2. Biomarker Endpoint Differences and CATE

Recently, the National Institute on Aging and the Alzheimer's Association updated their diagnostic criteria for AD, adapting to the increase in biomarker technology that is available and has been validated [6]. Several of the mentioned core AD biomarkers in the publication are included in our study, such as Aβ 42/40 ratio in the CSF, amyloid PET scan, p-Tau, as well as non-AD specific biomarkers such as MRI and FDG PET scans.

For bapineuzumab, CATE analysis found that various amyloid biomarkers were improved in association with the medication. In examining CSF Aβ 42/40, the MMSE and ADAS-Cog RP definition demonstrated a positive influence, while the CDR-SB did not. The CDR-SB and ADAS-Cog identified the amyloid PET scan as being positively influenced by bapineuzumab.

In RPs, the treatment seems to have slowed the endpoint accumulation of Aβ when compared to placebo, though not by a statistically significant amount. However, when performing the PIB PET scan SUVR $\geq$ 1.35 restricted analysis, RPs receiving treatment had a statistically significant increase in Aβ, indicating that the medication did not benefit RPs, which is consistent with our findings. For NRPs, there is less ambiguity, with bapineuzumab demonstrating statistical significance in the endpoint analysis and positive findings in the CATE analysis for the amyloid PET scan and CSF p-tau in the MMSE and ADAS-Cog RP definition analyses. This suggests that the extent of Aβ clearance may be a key factor in the differential response, as NRPs experienced an overall greater reduction in Aβ burden, which was associated with more significant clinical benefits. Given that RPs are, on average, more progressed both in terms of Aβ deposition and cognitively at baseline, we postulate that RPs could benefit from starting treatment earlier in their disease process. Furthermore, a majority of RPs are APOE4 carriers, and APOE4 carriers appeared to benefit more from the treatment than non-carriers in the bapineuzumab clinical trials [8]. In terms of non-specific biomarkers, MRI endpoint results showed some evidence that patients in the treatment group had more atrophy than the placebo group. This is consistent with a study on anti-Aβ immunotherapies that found these therapies were associated with brain atrophy results on MRI [18]. As a whole, RPs had more brain atrophy than NRPs in the placebo group. Interestingly, there were sparse statistically significant results in the endpoint analysis that demonstrated NRPs were more negatively affected by treatment than RPs by this treatment-associated brain atrophy. It is unclear why this would occur in the NRP group more than in the RP group. It is important to note that some of the MRI endpoint analysis shows that patients had atrophy on MRI, while the CATE analysis demonstrated that there was overall treatment benefit, especially in the NRP group. There could be a few explanations for this finding, including that the NRP group is heterogeneous where some patients may not have atrophy with treatment, however others may

actually worsen with treatment and have atrophy. CATE uses causal forests which focuses on learning this heterogeneity, therefore, even if the overall mean demonstrates atrophy, the CATE can still show benefits for subgroups within NRPs.

Semagacestat seemed to have consistent findings in the RP group having a positive effect on both Aβ 42/40 CSF and plasma levels. The NRP analysis showed benefit on Aβ CSF in the endpoint analysis and Aβ plasma, MRI, and FDG PET scan via the CATE analysis, suggesting a more favorable central response to the medication than RPs. In the original clinical trial, plasma levels of Aβ 42 and 40 decreased in the treatment group, however, CSF levels remained the same [7]. One hypothesis discussed by the authors is that the treatment worked peripherally, but not in the brain, as evidenced by lack of CSF and imaging positive outcomes. The trial also highlighted how semagacestat interfered with the cleavage of other substrates, including Notch, which is critical for synaptic signaling and neuroplasticity, and may contribute directly to cognitive worsening independent of amyloid reduction. Additionally, off-target binding could have caused negative effects that outweighed any improvements to biomarkers or cognition. Our findings indicate that RPs may be more vulnerable to the adverse cognitive effects of semagacestat, potentially due to a more aggressive disease trajectory, increased sensitivity to the Notch inhibiting activities, or the negative and strong off-target binding effects. Additionally, it was noted in the clinical trials that exposure to the higher dosages of semagacestat may have contributed to worsening cognition. Because we combined the two dosages into one single group in our analysis, we are unable to test if this was the case for RPs as well. Further analysis of the data should be conducted to determine whether there is a difference in adverse events between RPs and NRPs, given the toxic side effects of semagacestat.

4.3. Clinical Trials: Past and Future

Previous randomized clinical trials have identified RPs in post-hoc analyses, including aducanumab's. While aducanumab was designated for accelerated approval by the FDA because it was shown to decrease the amount of Aβ plaque in the brain, the cognitive benefit was mixed and only met primary or secondary endpoints in one of the two clinical trials [5,19,20]. However, it was argued that once patients who rapidly progressed were removed from the clinical trial, the CDR-SB (the primary objective) illustrated a slowing of decline amongst patients who were randomized to the high dose treatment. Importantly, although the primary pathway for FDA designated accelerated approval was Aβ reduction, the impact on the Aβ plaque or other biomarkers was not published in relation to RPs. Lastly, the FDA approved the use of aducanumab for accelerated approval whether a patient is considered an RP or not. The selective exclusion of RPs raises concerns about the generalizability of trial findings and the applicability of medications to real-world AD populations.

A post-hoc analysis conducted on another anti-Aβ medication, gantenerumab, also explored cognition in RPs [21]. This analysis showed that RPs were responsive to gantenerumab at higher doses via the cognitive tests ADAS-Cog 13, MMSE, and CANTAB (but not the CDR-SB). As with aducanumab, the treatment's effect on biomarkers was not published. Interestingly, similar to our study, the authors noticed that at baseline there were differences in characteristics between RPs and "slow progressors," and that the RPs seemed more progressed according to the FAQ, CDR-SB and MRI hippocampal volume.

The limited data on the pathological trends of RPs in AD and their response to treatment highlights the need for further studies, such as ours. Unfortunately, patients with RPs enrolled in clinical trials may experience more rapid cognitive decline due to inherent disease pathology rather than the effects of the drug being tested. It may be possible to identify these patients through biomarkers or progression rates in the clinic prior to clinical trial enrollment, which could help stratify them before randomizing treatment distribution. Furthermore, a concern is that in identifying RPs earlier in their disease process, pharmaceutical companies will want to exclude RPs from clinical trials, which would be unethical and could limit the generalizability of findings to the broader AD population. Retrospective analyses such as these allow 1) the validation of previously defined metrics of rapid progression, 2) identification of more clinical and biomarker features that reliably distinguish this subset of patients, and 3) better quantify the progression of decline. For example, these retrospective results suggest a need in future prospective therapeutic trials to balance NRPs and RPs between the treatment and placebo groups since their outcomes may differ. This would avoid a false positive or false negative outcome. Moreover, these results suggest that the choice of trial endpoints and expected effect sizes for the RPs may need to differ from the NRPs. Ideally, treatment trial companies could create an objective to identify RPs early on in the clinical trial and conduct further analyses on how medications affect RPs, giving them a similar chance at improving treatment outcomes as NRPs.

4.4. Limitations

Our study has several limitations. First, since we used data from clinical trials, the generalizability of this study is only to clinical trial participants and not the general population. Additionally, the clinical trial population overwhelmingly has more non-Hispanic white patients which is not representative of the symptomatic AD population [22].

Second, since the clinical trials were designed and conducted over a decade ago, we are limited by the technology, understanding of AD, and diagnostic tools from that time. There may be more differences between RPs and NRPs with newer tools, and as such, more research is needed with the new diagnostics to identify them and to understand why they progress so rapidly. Going forward, we plan to define a RP using clinical metrics, including our referenced cognitive definitions and expanding to clinical biomarker definitions as a result of these retrospective analyses. While there will be overlap between RPs and NRPs by nature of the disease, these results show that there is potential to define the differences between the two cohorts beyond baseline metrics.

Third, both clinical trials had an inclusion criterion that required patients to have an MMSE score of 16–26 at the first visit. The relatively low baseline MMSE score may have introduced a number of confounding factors within these trials. Increased disease heterogeneity may have led to variable treatment responses, especially for patients with more advanced disease.

Fourth, neither trial considered Aβ deposition in either the inclusion or exclusion criteria which could have also led to differences in treatment response. To address these issues, we conducted additional analyses that mirror contemporary inclusion and exclusion criteria. Restricting the sample to patients who were Aβ positive at baseline via PIB PET scan (eTable 11), and to patients with an MMSE > 20 at baseline (eTable 12) yielded some differences but generally produced results consistent with our primary analyses. However, further work using more recent clinical trial datasets with more modern biomarkers, and contemporary inclusion and exclusion criteria should be conducted.

Fifth, patients who received either the 140 mg or 100 mg dosage of semagacestat were combined into a single treatment group. Therefore, while a higher dosage exposure may have contributed to worsening cognition in the original trial, our data cannot distinguish whether the response between RPs and NRPs reflects exposure-related effects, or biological differences.

Finally, our RP definition uses cognitive assessment scores from baseline to the individual's end of study. Patients in the treatment group have been exposed to bapineuzumab or semagacestat, and therefore the treatment could hypothetically affect the number of patients in the RP group if the treatment modifies outcomes related to cognitive tests. In the case of semagacestat, the treatment was associated with worse cognitive outcomes, especially at higher doses. According to eTable 3, there were more RPs in the treatment group than in the placebo group. However, the rates of RPs in the treatment and placebo groups are

similar across all RP definitions and for both treatments. One method to counteract the issue is to create a model that predicts who will become an RP using only demographic and baseline data. Previous RP definitions that only use these data rely on the fact that RPs are typically more progressed at baseline than NRPs [23]. While we also found that, on average, an RP is more progressed at baseline, not everyone who is already progressed at baseline becomes an RP. Additionally, this definition is limited to clinical trials and therefore restricted by trial inclusion/exclusion criteria, as well as timing—specifically when the patient is diagnosed and able to enter the trial. Furthermore, the definition can still potentially be influenced by FDA approved treatments such as donepezil, galantamine, rivastigmine, or memantine, as patients can be on those treatments at baseline. While we have created a model to predict RPs, we found the best internal and external validity by using longitudinal data, specifically from baseline until week 28 [1]. Ideally, RPs would be identified at a clinic visit, prior to even being approached for a clinical trial. Data from presymptomatic clinical trials, or the clinical/ community setting would need to be utilized to avoid issues listed above.

4.5. Next Steps and Conclusion

Understanding the impact of RPs is crucial for refining AD clinical trial designs, as their imbalanced inclusion can significantly influence the assessment of treatment efficacy. Our study reveals that key biomarkers, such as CSF and plasma Aβ levels, as well as Aβ PET scan results, change in response to Aβ monoclonal antibody or γ-secretase inhibitor administration, supporting the possibility that RPs do respond to treatments. Previous research has shown that early administration of disease-modifying treatments leads to more favorable outcomes, and it is reasonable to expect that early identification of RPs and timely medication administration could slow their rate of disease progression. Future analysis should aim to identify RPs earlier in their disease process, determine whether RPs respond to treatment as NRPs do, and examine more possible explanations for why some AD patients progress so rapidly.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interests

XJ is CPRIT Scholar in Cancer Research (RR180012), and he was supported in part by Christopher Sarofim Family Professorship, UT Stars award, UTHealth startup, the National Institute of Health (NIH) under award number R01AG066749, R01AG066749–03S1, R01LM013712, R01LM014520, R01AG082721, R01AG066749, U01AG079847, U01TR002062, U01CA274576 and the National Science Foundation (NSF) #2,124,789.

YK is supported in part by National Institute of Health (NIH) under award number R01AG082721 and R01AG084637.

PS is funded by the McCord Family Professorship in Neurology, the Umphrey Family Professorship in Neurodegenerative Disorders, multiple NIH grants, several foundation grants, and contracts with multiple pharmaceutical companies related to the performance of clinical trials. He serves as a consultant and speaker for Eli Lilly, Biogen, and Acadia Pharmaceuticals.

No other authors have declarations to disclose.

Declaration of Generative AI and AI-assisted technologies in the writing process

None used.

CRediT authorship contribution statement

Kristofer Harris: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Madison Shyer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization. **Dulin Wang:** Writing – original draft, Methodology, Formal analysis, Data curation. **Elizabeth He:** Writing – review & editing, Writing – original draft. **Matias Cattani:** Writing – review & editing, Writing – original draft. **Catherine Zhang:** Writing – review & editing, Writing – original draft. **Christine M. Farrell:** Writing – review & editing, Data curation. **Xiaoqian Jiang:** Supervision, Resources, Funding acquisition. **Yejin Kim:** Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition. **Paul E. Schulz:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Paul Schulz reports a relationship with Eli Lilly and Company that includes: consulting or advisory. Paul Schulz reports a relationship with Biogen that includes: consulting or advisory. Paul Schulz reports a relationship with Acadia Pharmaceuticals Inc that includes: consulting or advisory. Christine Farrell reports a relationship with Eli Lilly and Company that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This publication is based on data contributed by Eli Lilly that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and Vivli and Eli Lilly are not in any way responsible for, the contents of this publication.

This study also used data obtained from the Yale University Open Data Access Project under YODA Project 2020–4323, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The interpretation and reporting of research using this data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100483.

References

[1] Ma X, Shyer M, Harris K, Wang D, Hsu YC, Farrell C, et al. Deep learning to predict rapid progression of Alzheimer's disease from pooled clinical trials: A retrospective study. PLOS Digit Health [Internet] 2024;3(4):e0000479. Apr 1 [cited 2025 Jul 8] Available from, https://journals.plos.org/digitalhealth/article?id=10.1371/journal.pdig.0000479.

[2] Geschwind MD, Haman A, Miller BL. Rapidly Progressive Dementia. Neurol Clin [Internet] 2007;25(3):783. Aug [cited 2025 Jul 8]Available from, https://pmc.ncbi.nlm.nih.gov/articles/PMC2706263/.

[3] Hermann P, Zerr I. Rapidly progressive dementias — aetiologies, diagnosis and management. Nat Rev Neurol 2022;18(6):363–76. 18:6 [Internet]. 2022 May 4 [cited 2025 Jul 8]Available from, https://www.nature.com/articles/s41582-022-00659-0.

[4] Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I. Rapidly Progressive Alzheimer Disease. Arch Neurol [Internet] 2011;68(9):1124–30. Sep 1 [cited 2025 Jul 8]Available from, https://jamanetwork.com/journals/jamaneurology/fullarticle/1107857.

[5] Vaz M, Silva V, Monteiro C, Silvestre S. Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities. Clin Interv Aging [Internet] 2022;17:797–810. https://doi.org/10.2147/CIA.S325026?download=true [cited 2025 Jul 8]Available from.
[6] Jack CR, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimer 19s Dement [Internet] 2024;20(8):5143–69. https://doi.org/10.1002/alz.13859. Aug 1 [cited 2025 Jul 8]Available from.
[7] Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med [Internet] 2013;369(4):341–50. Jul 25 [cited 2025 Jul 8]Available from, https://drive.google.com/file/d/1utPBAlCCncrafJaJ29gCc-Tygt2GnJn6/view?usp=sharing&usp=embed_facebook.
[8] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease. N Engl J Med [Internet] 2014;370(4):322–33. Jan 23 [cited 2025 Jul 8]Available from, https://drive.google.com/file/d/1KVTAg3G97mjOOljMiVX7REdisKc4WTpB/view?usp=sharing&usp=embed_facebook.
[9] Study details | Effects of LY450139, on the progression of Alzheimer's disease as compared With Placebo | ClinicalTrials.gov [Internet]. [cited 2025 Jul 8]. Available from: https://clinicaltrials.gov/study/NCT00762411#publications.
[10] Study details | Effect of LY450139 on the long term progression of Alzheimer's disease | ClinicalTrials.gov [Internet]. [cited 2025 Jul 8]. Available from: https://clinicaltrials.gov/study/NCT00594568.
[11] Study details | Bapineuzumab in patients with mild to moderate Alzheimer's disease (ApoE4 Carrier) | ClinicalTrials.gov [Internet] [cited, https://clinicaltrials.gov/study/NCT00575055; 2025.
[12] Study details | Bapineuzumab in patients with mild to moderate Alzheimer's disease (ApoE4 Non-Carrier) | ClinicalTrials.gov [Internet] [cited, https://clinicaltrials.gov/study/NCT00574132; 2025.
[13] Wager S, Athey S. Estimation and inference of heterogeneous treatment effects using random forests. J Am Stat Assoc [Internet] 2018;113(523):1228–42. Jul 3 [cited 2025 Jul 8]Available from, https://www.tandfonline.com/doi/abs/10.1080/01621459.2017.1319839.
[14] Wang D, Ling Y, Harris K, Schulz PE, Jiang X, Kim Y. Characterizing treatment non-responders vs. responders in completed Alzheimer's disease clinical Trials. medRxiv [Internet] 2023. Oct 30 [cited 2025 Jul 8]; Available from, http://www.ncbi.nlm.nih.gov/pubmed/37961216.
[15] Seidl JNT, Massman PJ. Rapidly versus slowly progressing patients with Alzheimer's disease: Differences in baseline cognition. Am J Alzheimers Dis Other Demen [Internet] 2015;31(4):318. Jun 1 [cited 2025 Jul 8]Available from, https://pmc.ncbi.nlm.nih.gov/articles/PMC10852819/.
[16] Toro CA, Zhang L, Cao J, Cai D. Sex differences in Alzheimer's disease: Understanding the molecular impact. Brain Res [Internet] 2019;1719:194–207. Sep 15 [cited 2025 Nov 27]Available from, https://pubmed.ncbi.nlm.nih.gov/31129153/.
[17] Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. Arch Gen Psychiatry [Internet] 2005;62(6):685–91. Jun [cited 2025 Nov 27]Available from, https://pubmed.ncbi.nlm.nih.gov/15939846/.
[18] Alves F, Kalinowski P, Ayton S. Accelerated brain volume loss caused by Anti–β-amyloid drugs: A systematic review and meta-analysis. Neurol [Internet] 2023;100(20):e2114. May 16 [cited 2025 Jul 8]Available from, https://pmc.ncbi.nlm.nih.gov/articles/PMC10186239/.
[19] Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. J Prev Alzheimer 19s Dis [Internet] 2022;9(2):197–210. Apr 1 [cited 2025 Jul 8] Available from, https://link.springer.com/article/10.14283/jpad.2022.30.
[20] Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer 19s Dement 2021;17(4):696–701. Apr 1.
[21] Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther [Internet] 2017;9(1). Dec 8 [cited 2025 Jul 8]Available from, https://pubmed.ncbi.nlm.nih.gov/29221491/.
[22] Alzheimer, Association. Alzheimer's association 2024 Alzheimer's disease facts and figures. 2023.
[23] Delor I, Charoin JE, Gieschke R, Retout S, Jacqmin P. Modeling Alzheimer's disease progression using disease onset time and disease trajectory concepts applied to CDR-SOB scores from ADNI. CPT Pharmacomet Syst Pharmacol [Internet] 2013;2(10):1–10. https://doi.org/10.1038/psp.2013.54. Oct 1 [cited 2025 Jul 8]Available from.