Supplementary Material

Potential Impact of Slowing Disease Progression in Early Symptomatic Alzheimer's Disease on Patient Quality of Life, Caregiver Time, and Total Societal Costs: Estimates Based on Findings from GERAS-US Study

Supplementary Table 1. Demographic characteristics: patients (outcome analysis set)

Characteristic	Total (N=222)	MCI (n=108)	MILD AD (n=114)	p*
Sex, n (%)				0.594
Female	113 (50.9)	57 (52.8)	56 (49.1)	
Male	109 (49.1)	51 (47.2)	58 (50.9)	
Age at index date (y), mean (SD)	69.3 (8.23)	68.9 (7.98)	69.6 (8.49)	0.513
Race, n (%)				0.746
White	202 (91.0)	100 (92.6)	102 (89.5)	
Black or African American	15 (6.8)	6 (5.6)	9 (7.9)	
Asian	5 (2.3)	2 (1.9)	3 (2.6)	
Education, n (%)				0.010
Less than high school	73 (32.9)	26 (24.1)	47 (41.2)	
High school or above	143 (64.4)	80 (74.1)	63 (55.3)	
Unknown	6 (2.7)	2 (1.9)	4 (3.5)	
Work status, n (%)				0.718
Yes	35 (15.8)	18 (16.7)	17 (14.9)	
No	183 (82.4)	89 (82.4)	94 (82.5)	
Unknown	4 (1.8)	1 (0.9)	3 (2.6)	
Living situation, n (%)				0.268
Non-institutionalized	117 (75.5)	54 (81.8)	63 (70.8)	
Limited home care	25 (16.1)	9 (13.6)	16 (18.0)	
Adult home care	9 (5.8)	3 (4.5)	6 (6.7)	
Long term/permanent institutionalization	4 (2.6)	0	4 (4.5)	
Number of comorbidities, median (min, max)	2.0 (0, 6)	2.0 (0, 6)	2.0 (0, 6)	0.574
Comorbidities, n (%)				
Depression	74 (33.3)	36 (33.3)	38 (33.3)	1.000
Sleep disorder	40 (18.0)	24 (22.2)	16 (14.0)	0.120
Diabetes	51 (23.0)	24 (22.2)	27 (23.7)	0.874
Coronary artery disease	22 (9.9)	10 (9.3)	12 (10.5)	0.824
Hypertension	132 (59.5)	61 (56.5)	71 (62.3)	0.413
Receiving AD medication, n (%)	91 (41.0)	44 (40.7)	47 (41.2)	1.000
Time since AD diagnosis (y), mean (SD)	1.0 (1.5)	0.9 (1.4)	1.1 (1.6)	0.298
Time since first symptoms, mean (SD)	2.6 (2.5)	2.8 (3.1)	2.4 (1.8)	0.236
MMSE, mean (SD)	26.0 (2.7)	27.4 (1.8)	24.6 (2.8)	<0.001
CFI, mean (SD)	56.6 (16.3)	48.7 (14.5)	64.1 (14.3)	<0.001
Total caregiver time (h/day), mean (SD)	5.3 (5.7)	2.6 (3.4)	7.8 (6.2)	<0.001

Total cost/month, mean (SD)	3388 (3568.3)	2414 (3631.4)	4311 (3263.0)	<0.001
ZBI, mean (SD)	16.8 (14.1)	13.8 (14.4)	19.6 (13.4)	0.002
BASQID, mean (SD)	54.2 (21.8)	63.3 (20.3)	45.6 (19.6)	<0.001

AD, Alzheimer's disease; BASQID, Bath Assessment of Subjective QoL in Dementia; CFI, Cognitive Function Instrument; Max, maximum; MCI, mild cognitive impairment due to AD; MILD AD, mild dementia due to AD; Min, Minimum; MMSE, Mini-Mental State Examination; N, number of patients in the analysis population; n, number of patients in the specified category; SD, Standard Deviation; ZBI, Zarit Burden Interview.

* p-value is from t-test for continuous variables and from Fisher's exact test for categorical variables between MCI and MILD AD groups based on non-missing observations.

Supplementary Table 2. Demographic characteristics: study partners (outcome analysis set)

Characteristic	Total (N=222)	MCI (n=108)	MILD AD (n=114)	p*
Sex, n (%)				0.067
Female	147 (66.2)	65 (60.2)	82 (71.9)	
Male	75 (33.8)	43 (39.8)	32 (28.1)	
Age at index date (y), mean (SD)	57.7 (16.2)	57.9 (17.1)	57.6 (15.4)	0.867
Education, n (%)				0.001
Less than high school	56 (25.2)	20 (18.5)	36 (31.6)	
High school graduate	38 (17.1)	13 (12.0)	25 (21.9)	
Some college	57 (25.7)	28 (25.9)	29 (25.4)	
College or above	70 (31.5)	47 (43.5)	23 (20.2)	
Unknown	1 (0.5)	0	1 (0.9)	
Study partner relationship, n (%)				0.666
Spouse	104 (46.8)	54 (50.0)	50 (43.9)	
Sibling	18 (8.1)	6 (5.6)	12 (10.5)	
Child	48 (21.6)	22 (20.4)	26 (22.8)	
Friend	29 (13.1)	14 (13.0)	15 (13.2)	
Other	23 (10.4)	12 (11.1)	11 (9.6)	
Study partner resides with patient, n (%)	165 (74.3)	73 (67.6)	92 (80.7)	0.031
Number of caregivers in addition to study partner, n (%)				0.101
Zero	149 (67.1)	80 (74.1)	69 (60.5)	
One	59 (26.6)	23 (21.3)	36 (31.6)	
More than one	14 (6.3)	5 (4.6)	9 (7.9)	

AD, Alzheimer's disease; MCI, mild cognitive impairment due to AD; MILD AD, mild dementia due to AD; N, number of study partner in the analysis population; n, number of study partner in the specified category; SD, standard deviation

* p-value is from t-test for continuous variables and from Fisher's exact test for categorical variables between MCI and MILD AD groups based on non-missing observations.

Supplementary Table 3. Potential improvements in HRQoL by slowing disease progression (as measured by MMSE): sensitivity analysis

Outcome	Patient Group	MMSE LSMC from Baseline to 36 Months	Coefficient of MMSE Change from Baseline to 36 Months (SE)	% Change in BASQID from Baseline to Month 36 Relative to Baseline (95% CI)	Change in BASQID from Baseline to Month 36 (95% CI)	BASQID Savings at Month 36 Compared with Observed Progression
BASQID Score	MCI	-1.92 (observed progression)	2.448 (0.370)	-7.4% (-9.6%, -5.2%)	-4.692 (-6.097, -3.286)	NA
		-1.53 (20% slowing)		-5.9% (-7.7%, -4.2%)	-3.753 (-4.878, -2.629)	0.938
		-1.44 (25% slowing)		-5.6% (-7.2%, -3.9%)	-3.519 (-4.573, -2.465)	1.173
		-1.34 (30% slowing)		-5.2% (-6.7%, -3.6%)	-3.284 (-4.268, -2.300)	1.407
	MILD AD	-3.68 (observed progression)	1.589 (0.313)	-12.8% (-17.8%, -7.8%)	-5.853 (-8.136, -3.570)	NA
		-2.95 (20% slowing)		-10.3% (-14.3%, -6.3%)	-4.683 (-6.509, -2.856)	1.171
		-2.76 (25% slowing)		-9.6% (-13.4%, -5.9%)	-4.390 (-6.102, -2.677)	1.463
		-2.58 (30% slowing)		-9.0% (-12.5%, -5.5%)	-4.097 (-5.695, -2.499)	1.756

AD, Alzheimer's disease; BASQID, Bath Assessment of Subjective QoL in Dementia; CI, confidence interval; HRQoL, health-related quality of life; LSMC, least squares mean change (from MMRM model); MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; MILD AD, mild dementia due to AD; NA, not applicable; SE, standard error.

Patients with both MMSE and outcomes measured at baseline visit and 36-month visit (outcome analysis set) were included in the analyses (change from baseline to 36 months). The linear regression model was performed for change in BASQID from baseline to 36 months. Separate models were fitted for MCI and MILD AD, respectively. All models included baseline value, change in MMSE from baseline to 36 months, age, number of comorbidities, and study partner relationship.

Supplementary Table 4. Potential cost and caregiver time savings by slowing disease progression (as measured by MMSE): sensitivity analysis

Outcome	Patient Group	MMSE LSMC from Baseline to 36 Months	Coefficient of MMSE Change from Baseline to 36 Months (SE)	% Increase in Total Outcome Over 36 Months Relative to No Progression (95% CI)	Increase in Total Outcome Over 36 Months Relative to No Progression (95% CI)	Total Outcome Savings Over 36 Months Compared with Observed Progression
Total caregiver time (RUD)	MCI	-1.92 (observed progression)	-502.8 (74.7)	27.7% (19.5%, 35.8%)	963.7 (679.5, 1247.9)	NA
		-1.53 (20% slowing)		22.1% (15.6%, 28.7%)	771.0 (543.6, 998.4)	192.7
		-1.44 (25% slowing)		20.7% (14.6%, 26.9%)	722.8 (509.6, 936.0)	240.9
		-1.34 (30% slowing)		19.4% (13.7%, 25.1%)	674.6 (475.7, 873.6)	289.1
	MILD AD	-3.68 (observed progression)	-467.1 (80.4)	20.7% (13.6%, 27.7%)	1720.8 (1133.8, 2307.9)	NA
		-2.95 (20% slowing)		16.5% (10.9%, 22.2%)	1376.7 (907.0, 1846.3)	344.2
		-2.76 (25% slowing)		15.5% (10.2%, 20.8%)	1290.6 (850.3, 1730.9)	430.2
		-2.58 (30% slowing)		14.5% (9.5%, 19.4%)	1204.6 (793.7, 1615.5)	516.2
Total societal cost	MCI	-1.92 (observed progression)	-0.046 (0.019)	9.3% (1.6%,17.6%)	$7898 ($1379, $14911)	NA
		-1.53 (20% slowing)		7.4% (1.3%,13.8%)	$6262 ($1101, $11732)	$1636
		-1.44 (25% slowing)		6.9% (1.2%,12.9%)	$5857 ($1032, $10954)	$2041
		-1.34 (30% slowing)		6.4% (1.1%,12.0%)	$5454 ($963, $10181)	$2444
	MILD AD	-3.68 (observed progression)	-0.024 (0.008)	9.4% (3.6%,15.5%)	$11362 ($4349, $18766)	NA
		-2.95 (20% slowing)		7.4% (2.9%,12.2%)	$9007 ($3467, $14794)	$2354
		-2.76 (25% slowing)		6.9% (2.7%,11.4%)	$8425 ($3247, $13819)	$2937
		-2.58 (30% slowing)		6.5% (2.5%,10.6%)	$7846 ($3028, $12850)	$3516

AD, Alzheimer's disease; CI, confidence interval; GLM, generalized linear model; LSMC, least squares mean change (from MMRM model); MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment; MILD AD, mild dementia due to AD; NA, not applicable; RUD, Resource Utilization in Dementia questionnaire; SE, standard error.

Patients with both MMSE and outcomes measured at baseline visit and 36-month visit (outcome analysis set) were included in the analyses (total over 36 months). The general linear model was performed for total caregiver time. The GLM with log link and gamma distribution was performed for total societal cost. Separate models were fitted for MCI and MILD AD, respectively. All models included baseline MMSE, change in MMSE from baseline to 36 months, age, number of comorbidities, and study partner relationship.
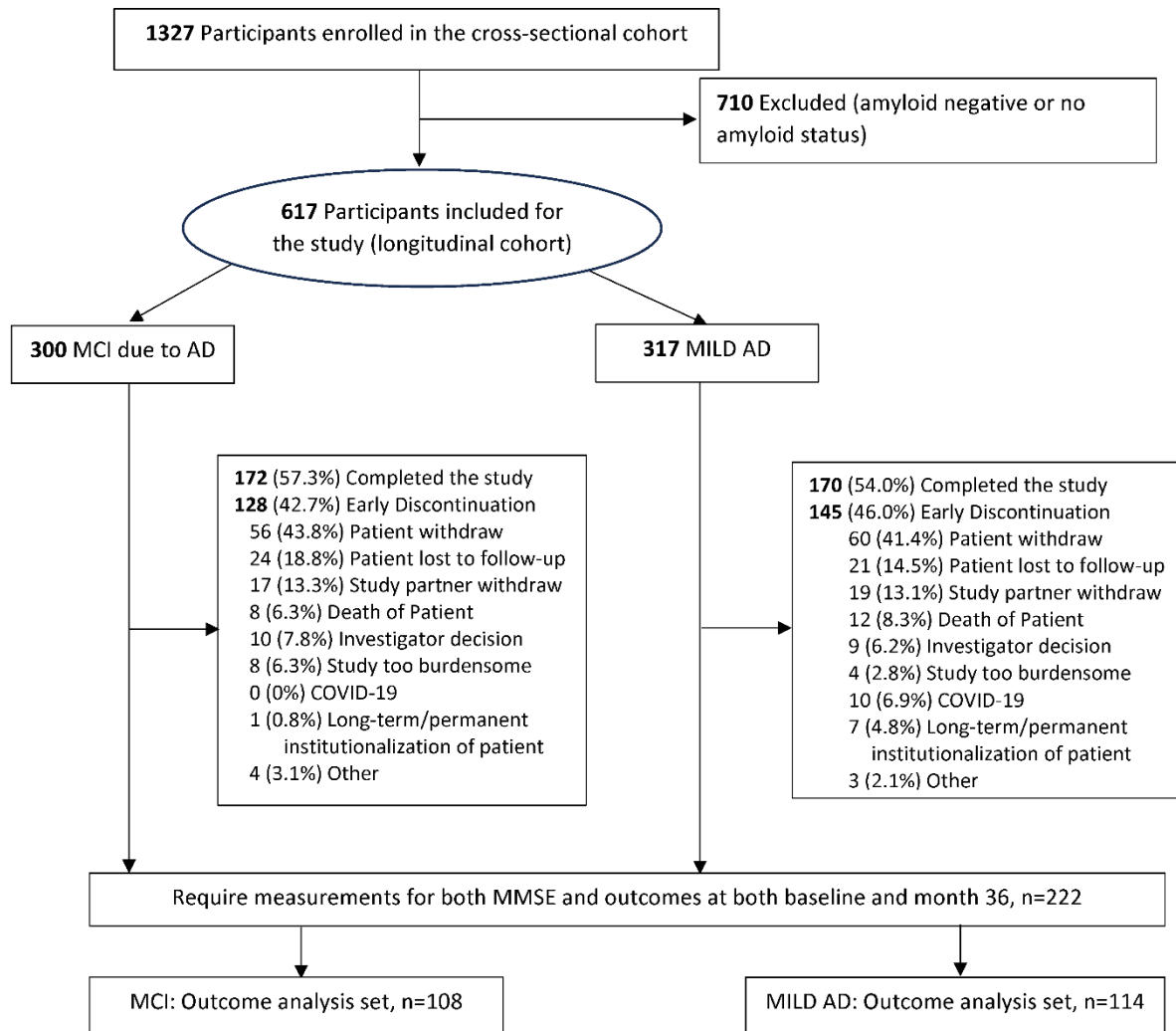
Caregiver time capped at 540 hours/month.

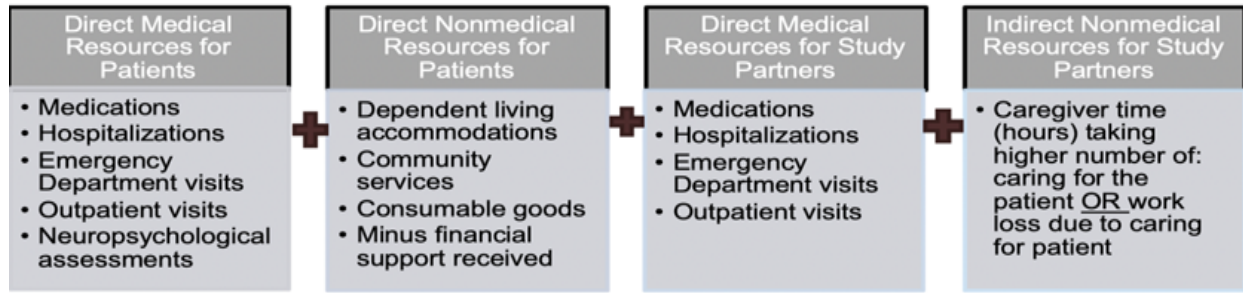**Supplementary Figure 1.** GERAS-US study design
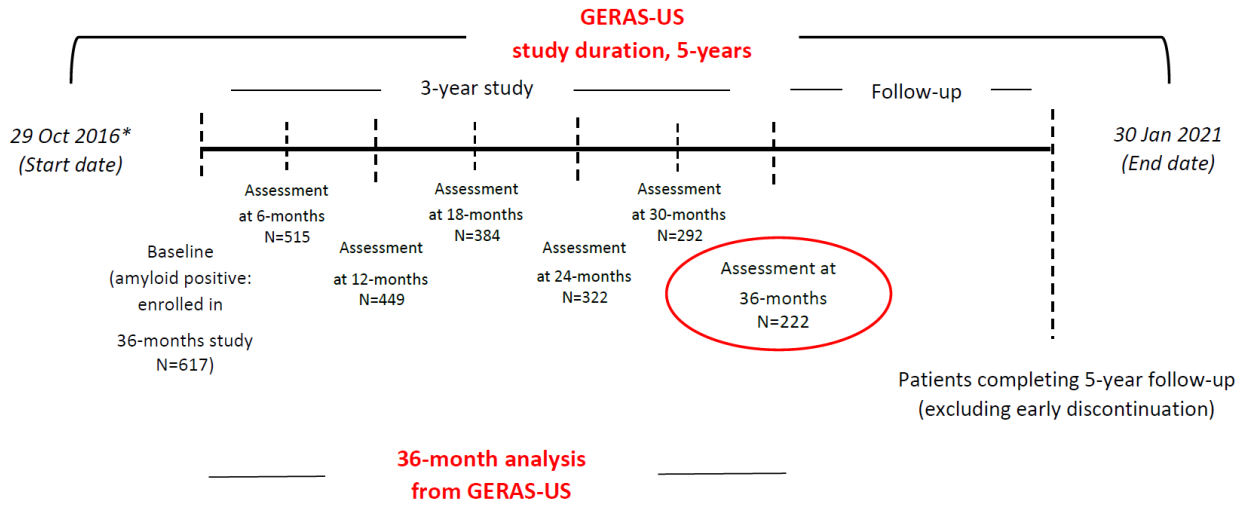
Jan, January; N, number of patients assessed using MMSE at each visit; Oct, October.

Supplementary Figure 2. Patient disposition and study population

1327 Participants enrolled in the cross-sectional cohort

710 Excluded (amyloid negative or no amyloid status)

617 Participants included for the study (longitudinal cohort)

300 MCI due to AD

317 MILD AD

172 (57.3%) Completed the study
128 (42.7%) Early Discontinuation
   56 (43.8%) Patient withdraw
   24 (18.8%) Patient lost to follow-up
   17 (13.3%) Study partner withdraw
   8 (6.3%) Death of Patient
   10 (7.8%) Investigator decision
   8 (6.3%) Study too burdensome
   0 (0%) COVID-19
   1 (0.8%) Long-term/permanent
      institutionalization of patient
   4 (3.1%) Other

170 (54.0%) Completed the study
145 (46.0%) Early Discontinuation
   60 (41.4%) Patient withdraw
   21 (14.5%) Patient lost to follow-up
   19 (13.1%) Study partner withdraw
   12 (8.3%) Death of Patient
   9 (6.2%) Investigator decision
   4 (2.8%) Study too burdensome
   10 (6.9%) COVID-19
   7 (4.8%) Long-term/permanent
      institutionalization of patient
   3 (2.1%) Other

Require measurements for both MMSE and outcomes at both baseline and month 36, n=222

MCI: Outcome analysis set, n=108

MILD AD: Outcome analysis set, n=114

Supplementary Figure 3. Components of total societal costs per month [16]

Direct Medical Resources for Patients	Direct Nonmedical Resources for Patients	Direct Medical Resources for Study Partners	Indirect Nonmedical Resources for Study Partners
• Medications • Hospitalizations • Emergency Department visits • Outpatient visits • Neuropsychological assessments	• Dependent living accommodations • Community services • Consumable goods • Minus financial support received	• Medications • Hospitalizations • Emergency Department visits • Outpatient visits	• Caregiver time (hours) taking higher number of: caring for the patient OR work loss due to caring for patient

Supplementary Figure 4. HRQoL by BASQID: LSMC baseline to 36 months
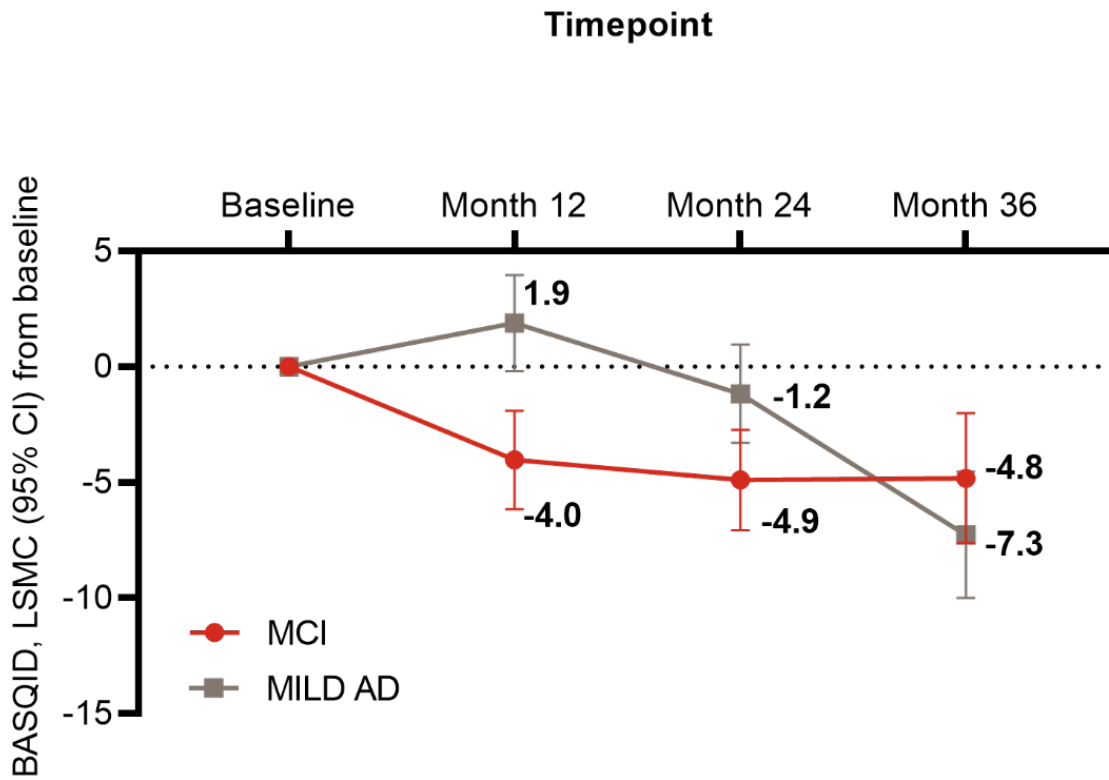
AD, Alzheimer's disease; BASQID, Bath Assessment of Subjective QoL in Dementia; CI, confidence interval; MCI, mild cognitive impairment; MILD AD, mild dementia due to AD; LSMC, least squares mean change (from MMRM model); MMRM, mixed model repeated measures.