Study 301: The Confirmatory Study to Verify and Describe the Clinical Benefit of Lecanemab for the Treatment of Early AD

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

Eisai Inc.

June 9, 2023

Introduction

Lynn Kramer, MD, FAAN

Chief Clinical Officer

Alzheimer's Disease and Brain Health

Eisai Inc.

Confirmatory Study 301 Fulfills Accelerated Approval Requirement

Accelerated Approval

Study 201
(Phase 2b)

Global, randomized, placebo controlled study in patients with MCI Due to AD or Mild AD Dementia

Lecanemab vs Placebo

N = 856

Confirmatory Study

Study 301
(Phase 3)

Global, randomized, placebo controlled study in patients with MCI Due to AD or Mild AD Dementia

Lecanemab vs Placebo

N = 1795

MCI = mild cognitive impairment, AD = Alzheimer's disease

Lecanemab: Confirmatory Study 301 Demonstrated Consistent, Persistent, Slowing of Disease Progression in Patients With Early AD

Selectively targets amyloid beta (Aβ) protofibrils

Highly statistically significant and clinically meaningful slowing in multiple measures of clinical decline, and effects on biomarkers consistent with slowing of disease progression

Well-tolerated with well-characterized safety, supporting a positive benefit-risk profile

Conducted in patients with broad range of comorbidities and concomitant medications from a diverse racial and ethnic background, clinical trial practice settings generalizable to US population

Introduction	**Lynn Kramer, MD, FAAN** Chief Clinical Officer Alzheimer's Disease and Brain Health / Eisai Inc.
Study 301 Efficacy	**Michael Irizarry, MD, MPH** SVP, Deputy Chief Clinical Officer Alzheimer's Disease and Brain Health / Eisai Inc.
Robustness of Efficacy Results	**Shobha Dhadda, PhD** SVP, Global Head, Biostatistics and Clinical Dev Operations Alzheimer's Disease and Brain Health / Eisai Inc.
Study 301 Safety	**Michael Irizarry, MD, MPH**
Clinician's Perspective	**Sharon Cohen, MD, FRCPC** Medical Director and Site Principal Investigator Toronto Memory Program
Conclusion	**Lynn Kramer, MD, FAAN**

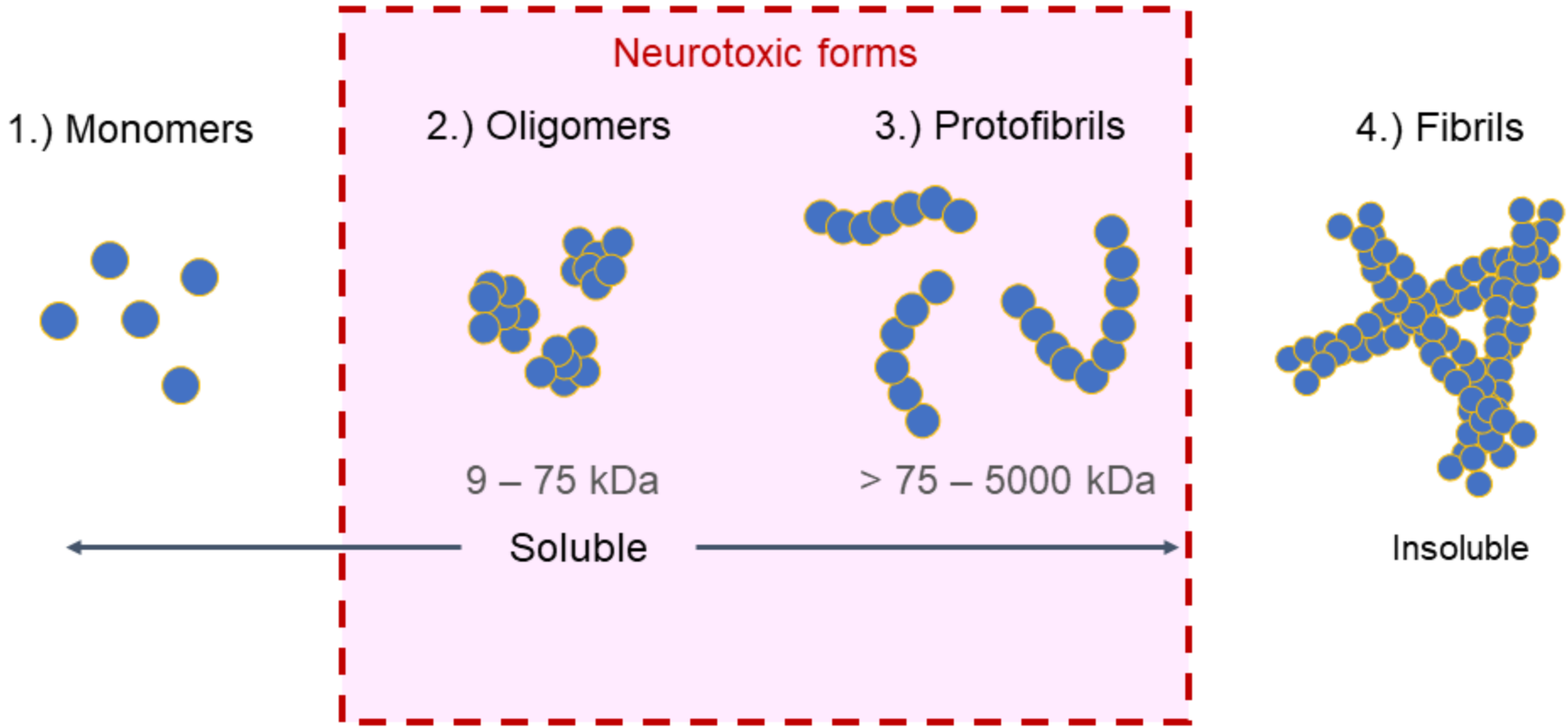
Alzheimer's Disease: Complex Clinical and Biological Continuum Beginning 10-20 Years Before Symptoms

- 6-7 million (~1 in 9) Americans aged 65 and older suffer from AD
  - 6th leading cause of death in US
- Amyloid accumulation is earliest detectable event, followed by tau hyperphosphorylation
  - Synaptic and neuronal loss
- Cognition, daily function, neuropsychiatric symptoms increase as disease progresses
  - Severe impact on patients, families, and healthcare systems

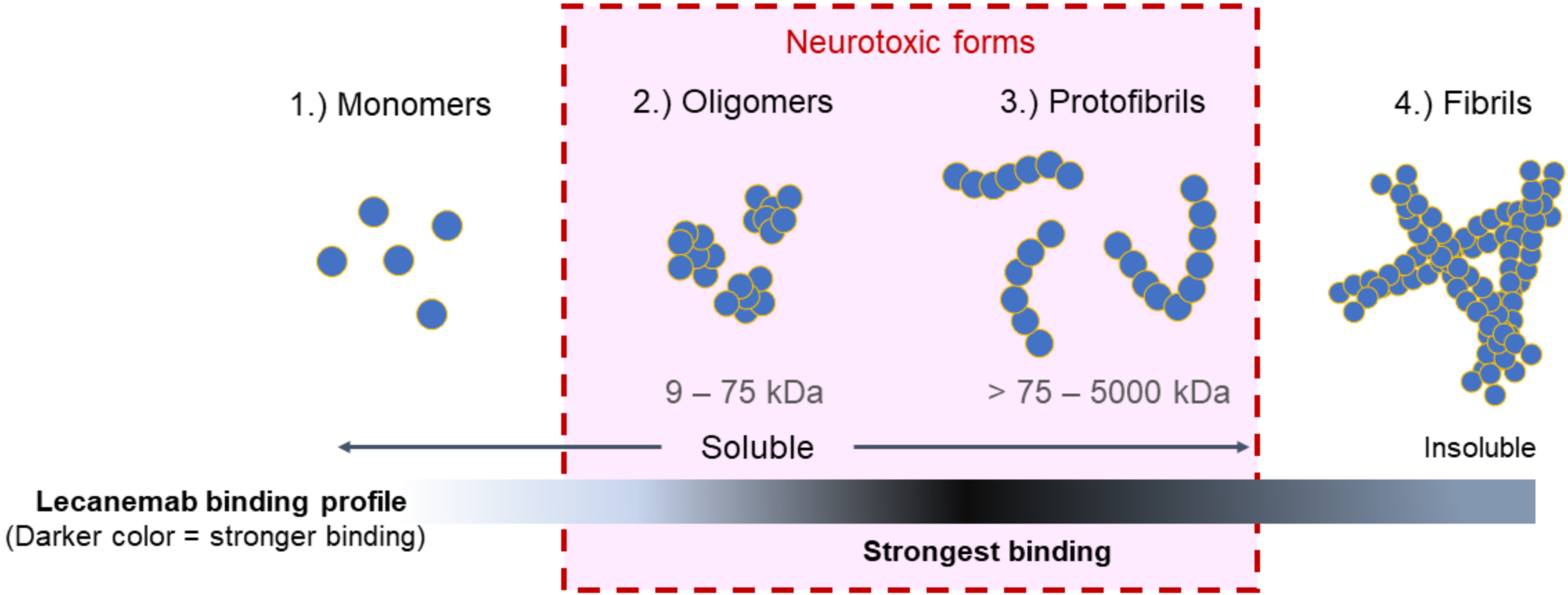
No Treatments That Slow Disease Progression With Broad Access

- Established treatments are insufficient
  - Currently established therapies treat symptoms, not pathophysiology or disease progression
    - Cholinesterase inhibitors; glutamate modulator
  - Provide modest, temporary benefit to symptoms
- No treatments approved for pre-dementia (MCI) stage of AD

Aβ Pathway: Aβ Dynamically Evolves Through Different Conformational States



Lecanemab: Unique Selectivity Towards Toxic Soluble Species of Aβ



- **Lecanemab**: Humanized immunoglobulin G1 (IgG1) monoclonal antibody
  - Selectively targets neurotoxic forms of soluble Aβ oligomers and protofibrils

Lecanemab Regulatory History

2009	Clinical Development Program Initiated
2021	Breakthrough Therapy and Fast Track Designations
2021	Rolling BLA Submission Under Accelerated Approval Pathway Based on Study 201
2021	Agreement that Study 301 Would Provide Confirmatory Evidence for Accelerated Approval Requirement
January 2023	Accelerated Approval for Treatment of Alzheimer's Disease with Confirmatory Study Requirement sBLA Submission Containing Results of Study 301

Study 301 Efficacy

Michael Irizarry, MD, MPH

Senior Vice President
Deputy Chief Clinical Officer
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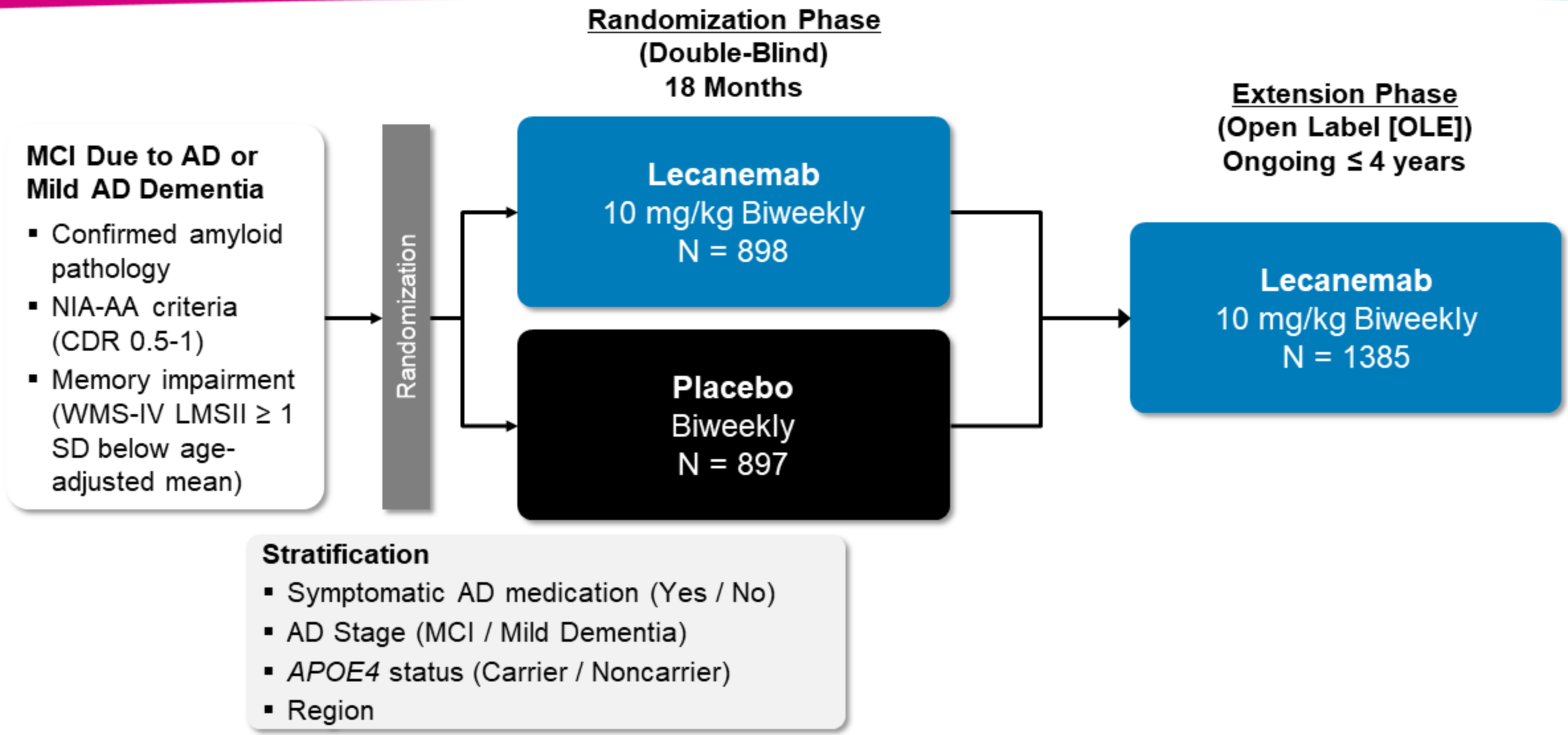
Eisai Inc.

Study 301: Confirmatory Study Design



NIA-AA = National Institute on Aging and Alzheimer's Association; WMS-IV LMSII = Wechsler Memory Scale IV-Logical Memory (subscale) II

Study 301: Statistical Testing Hierarchy (Change from Baseline at 18 Months)

Primary Endpoint (Primary and Key Secondary Endpoints Hierarchically Tested)
Clinical Dementia Rating – Sum of Boxes (CDR-SB)
Key Secondary Endpoints
1. Amyloid PET Centiloids
2. AD Assessment Scale – Cognitive subscale with 14 tasks (ADAS-Cog14)
3. AD Composite Score (ADCOMS)
4. AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL)
Prespecified Patient Reported Outcomes (PROs)
▪ European QOL-5 Dimensions (EQ-5D-5L)
▪ Quality of Life in AD (QOL-AD) – Patient Assessment
▪ Zarit Burden Interview (ZBI) – Care Partner

Baseline assessment defined as last measurement before first dose of lecanemab

Validated and Well Accepted Clinical Endpoints Measure Global Change in Cognition and/or Function

Endpoint (Change from Baseline)	Source	# Domains or Items	Assessment	Score Range	Worsening Score
CDR-SB	Patient and care partner	6 domains	Cognitive and functional	0-18	Higher
ADAS-Cog14	Patient	14 items	Cognitive	0-90	Higher
ADCS MCI-ADL	Care partner	24 items	Daily activities	0-53	Lower
ADCOMS	Composite of CDR-SB, ADAS-Cog14 and MMSE	12 items	Cognitive and functional	0-1.97	Higher

Endpoints validated across languages

MMSE = Mini-Mental State Examination

Study 301: Patient Disposition

Randomized and Treated
N = 1795

Placebo N = 897		**Lecanemab** N = 898	
Discontinued from Study	16%	Discontinued from Study	19%
Adverse event	3%	Adverse event	6%
Patient choice	3%	Patient choice	3%
Lost to follow-up	0.6%	Lost to follow-up	0.4%
Withdrawal of consent	7%	Withdrawal of consent	8%
Other	2%	Other	2%
Completed Double-Blind Study	**84%**	**Completed Double-Blind Study**	**81%**

Values rounded

Study 301: Baseline Characteristics Similar Across Groups

Characteristic	Placebo N = 875	Lecanemab N = 859
Age, years, mean (SD)	**71.0** (7.8)	**71.4** (7.9)
Female	**53%**	**52%**
CDR Global = 0.5	**81%**	**81%**
MMSE, mean (SD)	**25.6** (2.2)	**25.5** (2.2)
AD Stage		
MCI	**62%**	**61%**
Mild Dementia	**38%**	**39%**
***APOE4* Status**		
Noncarrier	**31%**	**31%**
Carrier	**69%**	**69%**
Heterozygous	**53%**	**53%**
Homozygous	**15%**	**16%**
Symptomatic AD Medication (AChEIs and/or memantine)	**53%**	**52%**

Values rounded; SD = standard deviation

Study 301: Diverse Baseline Characteristics

Characteristic	Combined Total (PBO+LEC) N = 1795	United States N = 947
Race		
Asian	17%	< 1%
Black	3%	5%
Caucasian	77%	95%
Other	4%	< 1%
Ethnicity		
Hispanic or Latino	13%	22%
Comorbidities		
Hypertension	55%	65%
Hyperlipidemia	60%	71%
Ischemic Heart Disease	16%	20%
Diabetes	15%	19%
Obesity	17%	24%
≥ 2 Comorbidities Listed Above	51%	64%
Concomitant medications		
Anticoagulants	5%	6%
Antiplatelet Therapy	27%	33%
Antidepressants	29%	30%

Values rounded; PBO = placebo, LEC = lecanemab

Study 301: Well-Balanced Baseline Clinical Characteristics

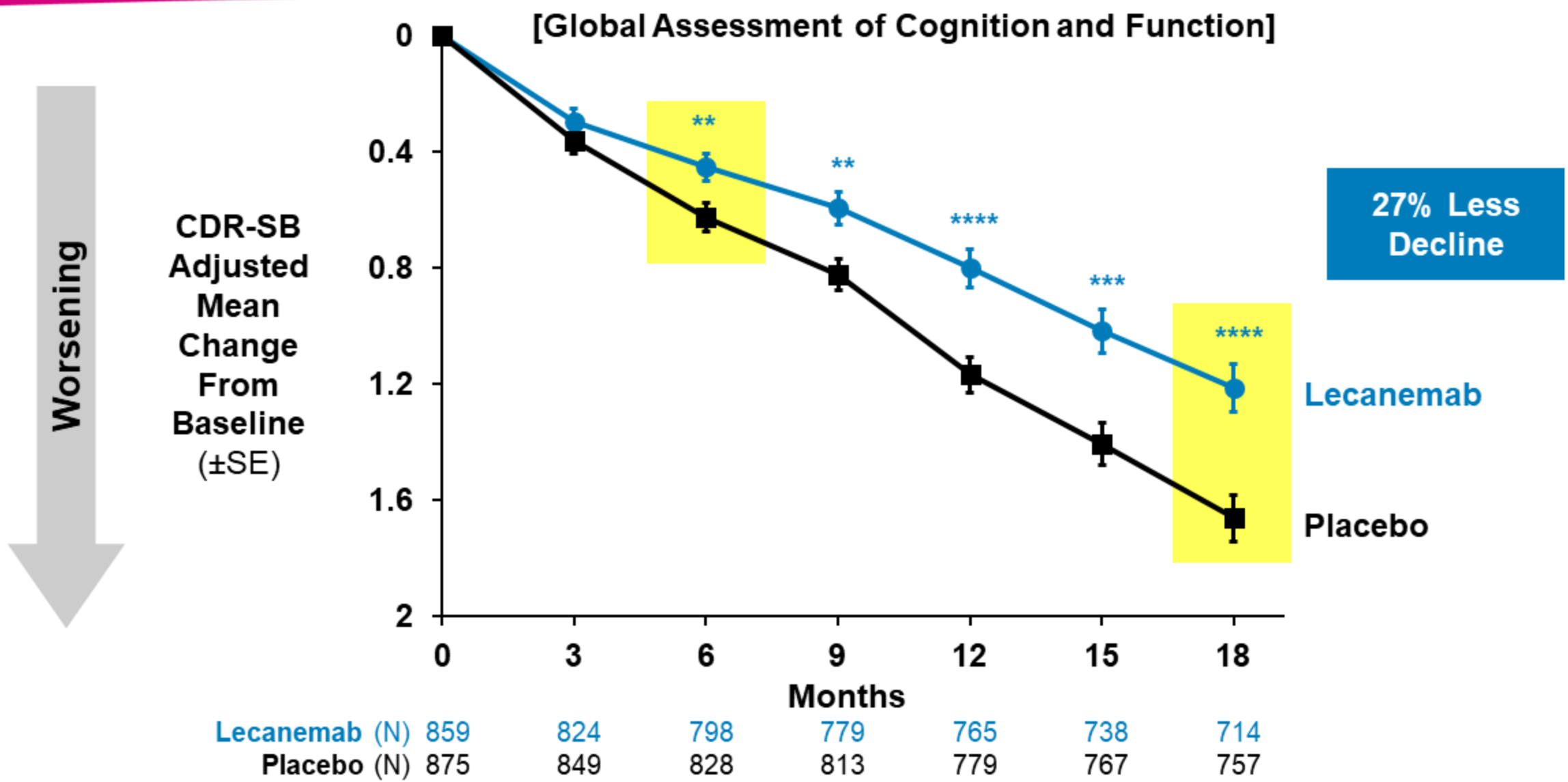
Endpoints	Placebo N = 875	Lecanemab N = 859
CDR-SB, mean (SD) [Scale range: 0 (best) - 18 (worst)]	**3.22** (1.343)	**3.17** (1.340)
Amyloid PET Centiloids, mean (SD)	**75.03** (41.82)	**77.92** (44.84)
ADAS-Cog14, mean (SD) [Scale range: 0 (best) - 90 (worst)]	**24.37** (7.561)	**24.45** (7.082)
ADCOMS, mean (SD) [Scale range: 0 (best) – 1.97 (worst)]	**0.400** (0.15)	**0.398** (0.15)
ADCS MCI-ADL, mean (SD) [Scale range: 0 (worst) – 53 (best)]	**40.9** (6.89)	**41.2** (6.61)

Study 301: Highly Statistically Significant Results for Primary and Key Secondary Endpoints

Endpoint	Measure, change from baseline at 18 months	Lecanemab vs Placebo mITT FAS+
Primary Efficacy	**CDR-SB**	
	Difference in Adjusted Mean (95% CI)	**-0.451** (-0.669, -0.233)
	p-value vs placebo	0.00005
Key Secondary Efficacy	**Amyloid PET Centiloids**	
	Difference in Adjusted Mean (95% CI)	**-59.12** (-62.64, -55.60)
	p-value vs placebo	< 0.00001
	ADAS-Cog14	
	Difference in Adjusted Mean (95% CI)	**-1.442** (-2.270, -0.613)
	p-value vs placebo	0.00065
	ADCOMS	
	Difference in Adjusted Mean (95% CI)	**-0.050** (-0.074, -0.027)
	p-value vs placebo	0.00002
	ADCS MCI-ADL	
	Difference in Adjusted Mean (95% CI)	**2.016** (1.208, 2.823)
	p-value vs placebo	< 0.00001

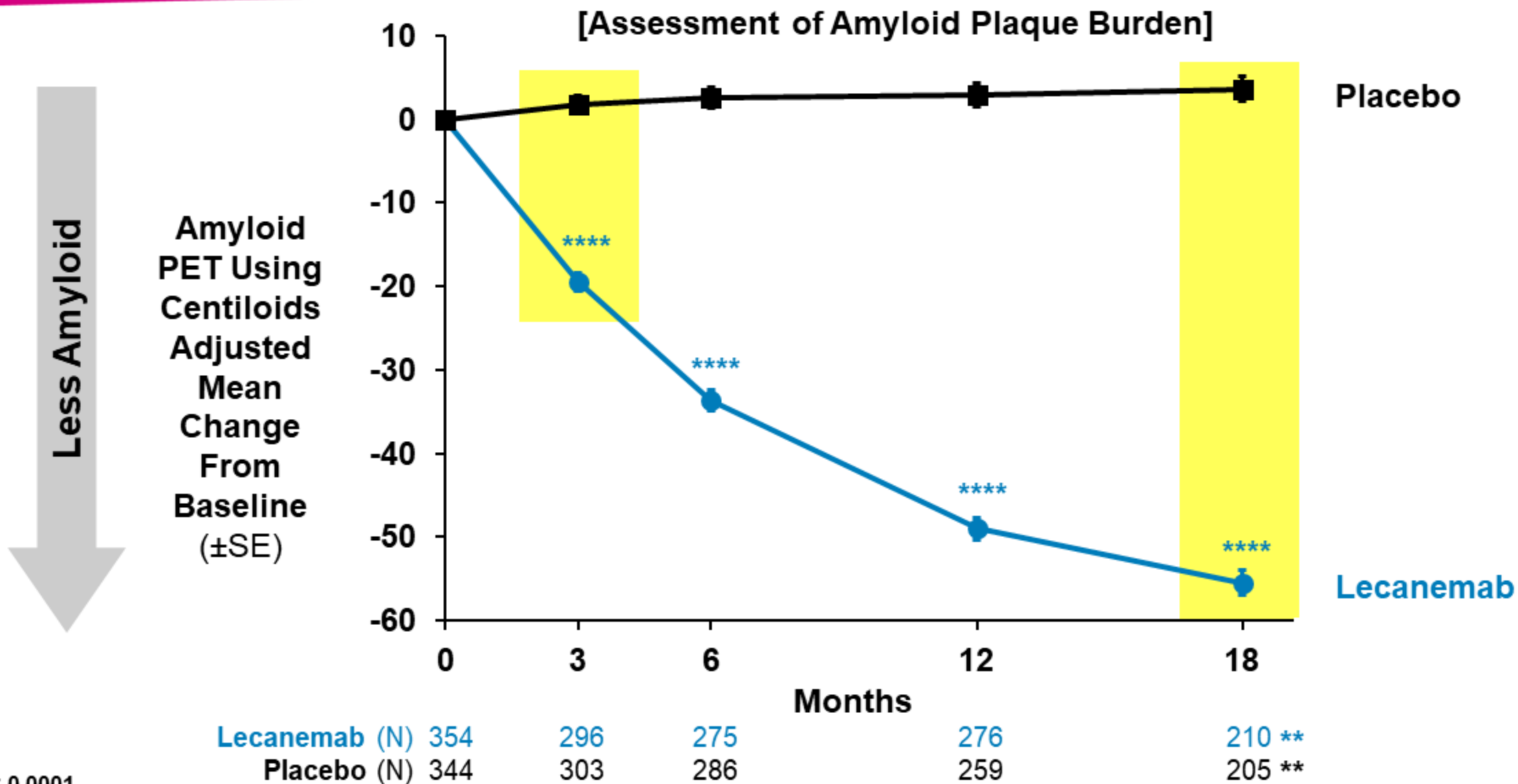
mITT = modified intent to treat, FAS = full analysis set, CI = confidence interval

Study 301 Primary Endpoint: Lecanemab Significantly Slowed Disease Progression by 27% on CDR-SB at 18 Months



**p < 0.01; ***p < 0.001; ****p < 0.0001; SE = standard error

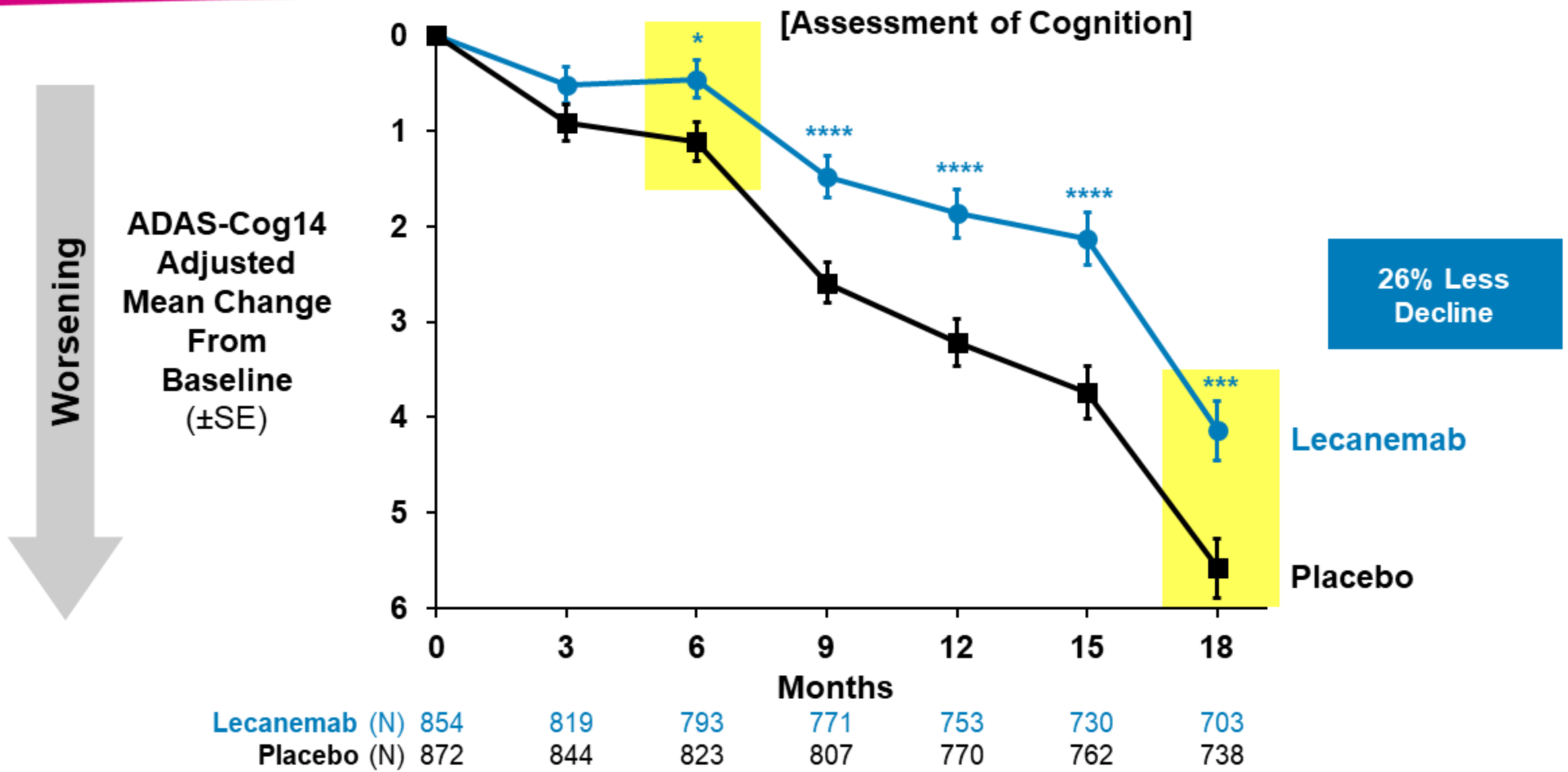
Study 301: Treatment with Lecanemab Significantly Reduced Amyloid at All Time Points 3 Months and Beyond



****p < 0.0001

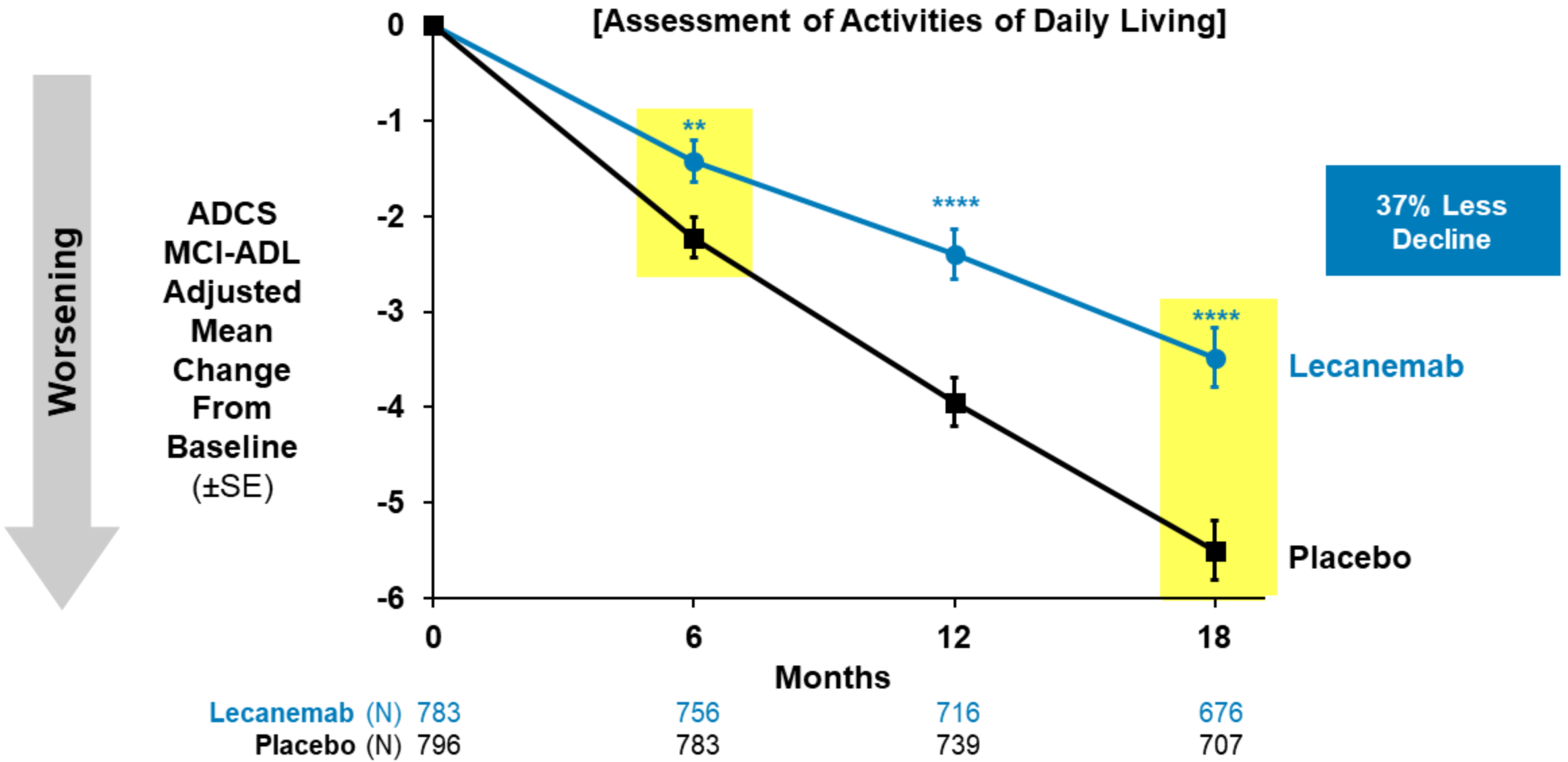
**73 patients not included at 18 months (per Statistical Analysis Plan) since PET assessments were performed after receiving lecanemab in open-label extension

Study 301: Lecanemab Significantly Slowed Disease Progression by 26% on ADAS-Cog14 at 18 Months



*p < 0.05; ***p < 0.001; ****p < 0.0001

Study 301: Lecanemab Significantly Slowed Disease Progression by 37% on ADCS MCI-ADL at 18 Months



**p < 0.01; ****p < 0.0001

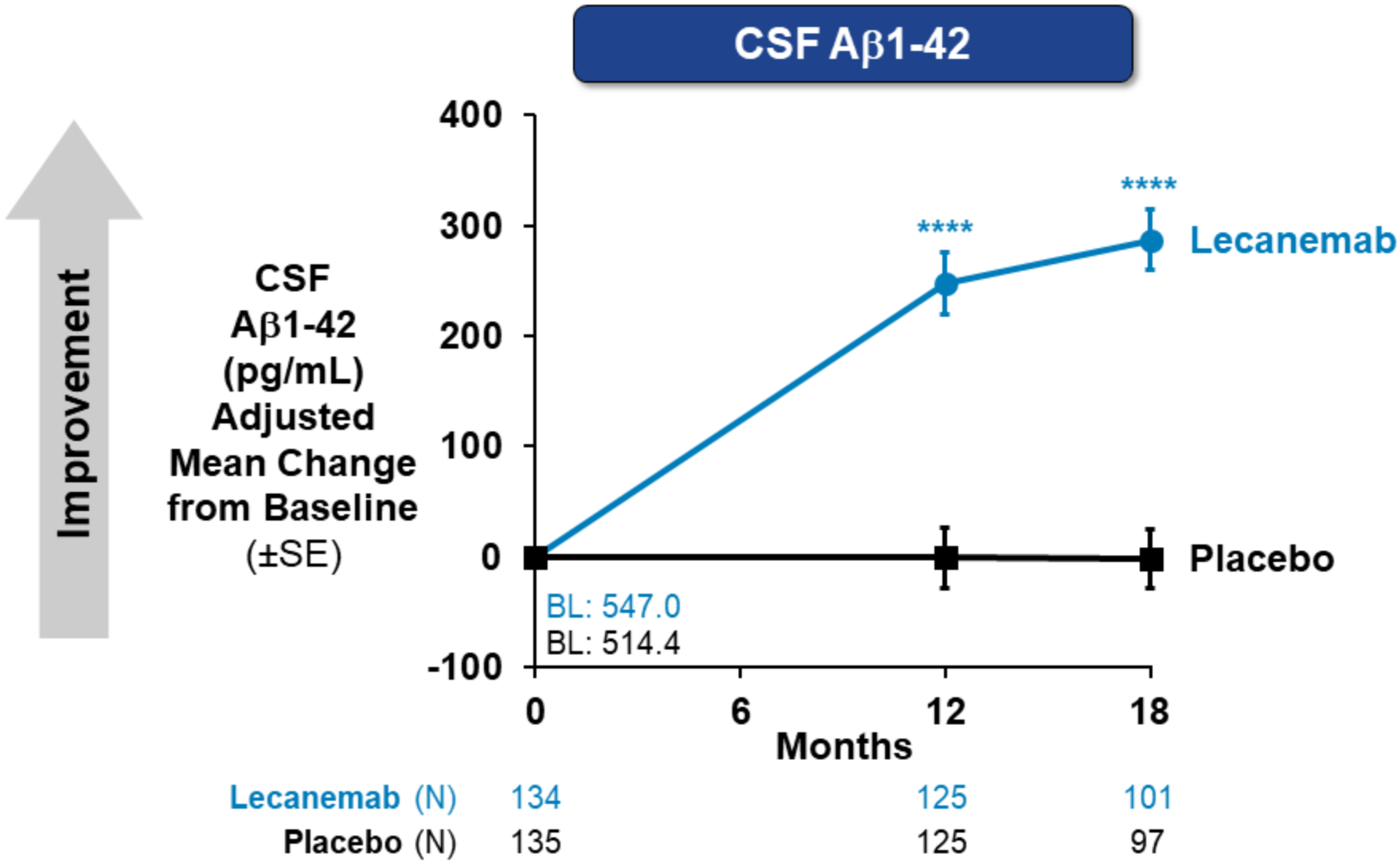
Biomarker Results Align with Clinical Outcomes That Support Slowing of Disease Progression

Biomarkers*

- Amyloid
- Tau
- Neurodegeneration/gliosis

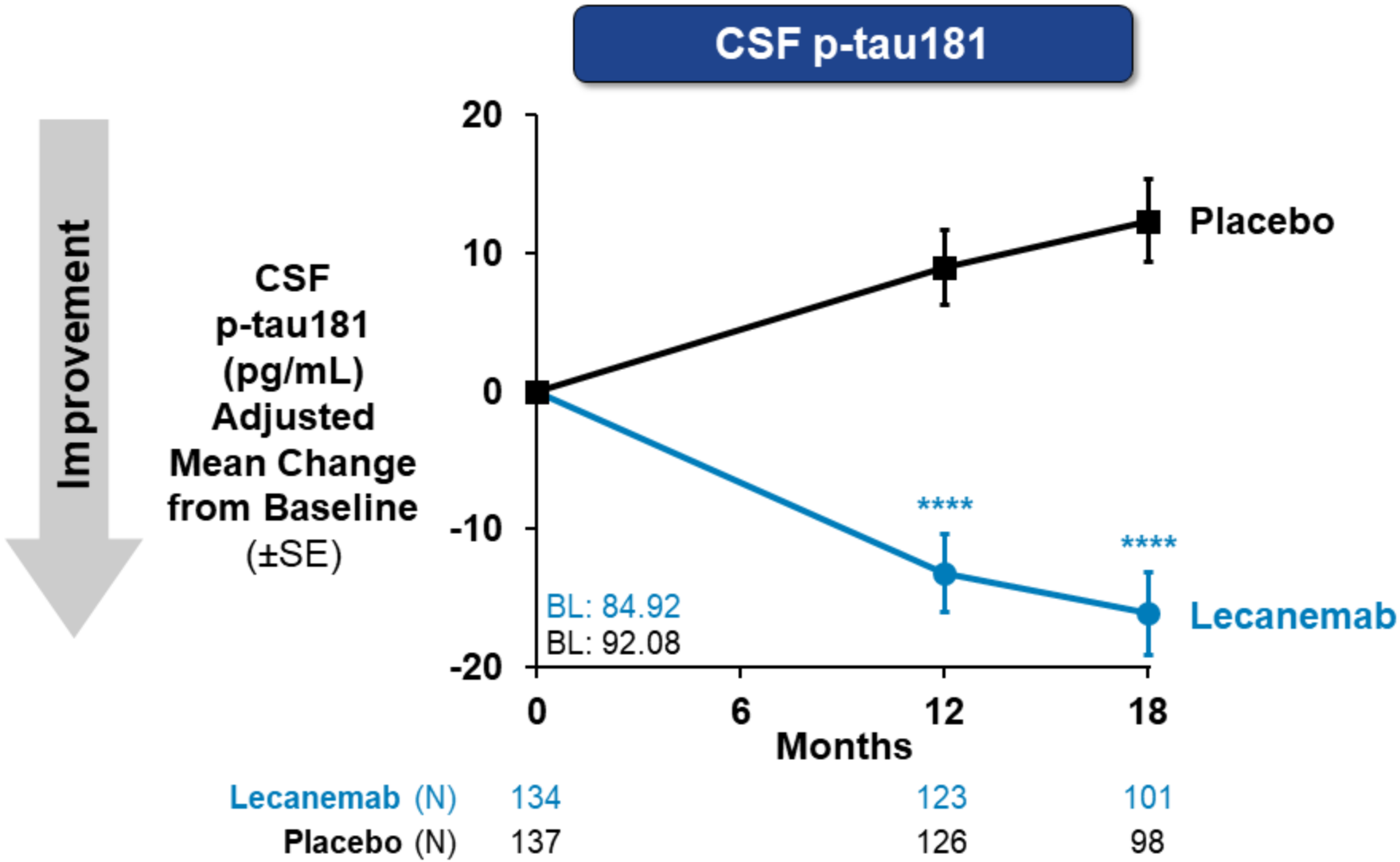
*Biomarkers discussed in briefing document, demonstrating effect on underlying disease pathophysiology

Study 301: Amyloid Biomarker Results Consistent With Effect on Underlying Disease Biology



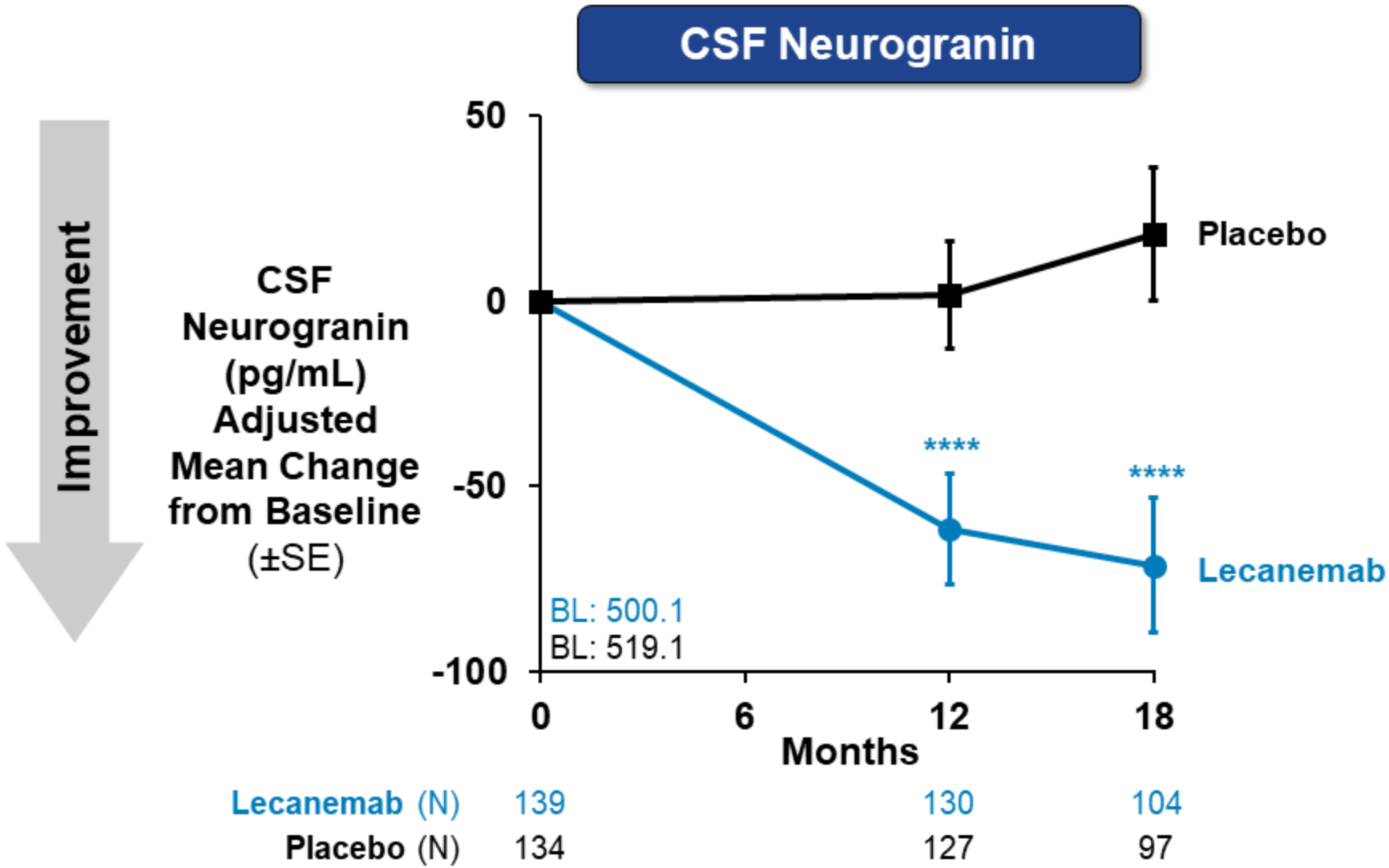
****p < 0.0001. BL= baseline, CSF = cerebral spinal fluid

Study 301: Tau Biomarker Results Consistent With Effect on Underlying Disease Biology



****p < 0.0001. p-tau181 = phosphorylated-tau181

Study 301: Neurodegeneration/Gliosis Biomarker Results Consistent With Effect on Underlying Disease Biology



****p < 0.0001

Robustness of Efficacy Results

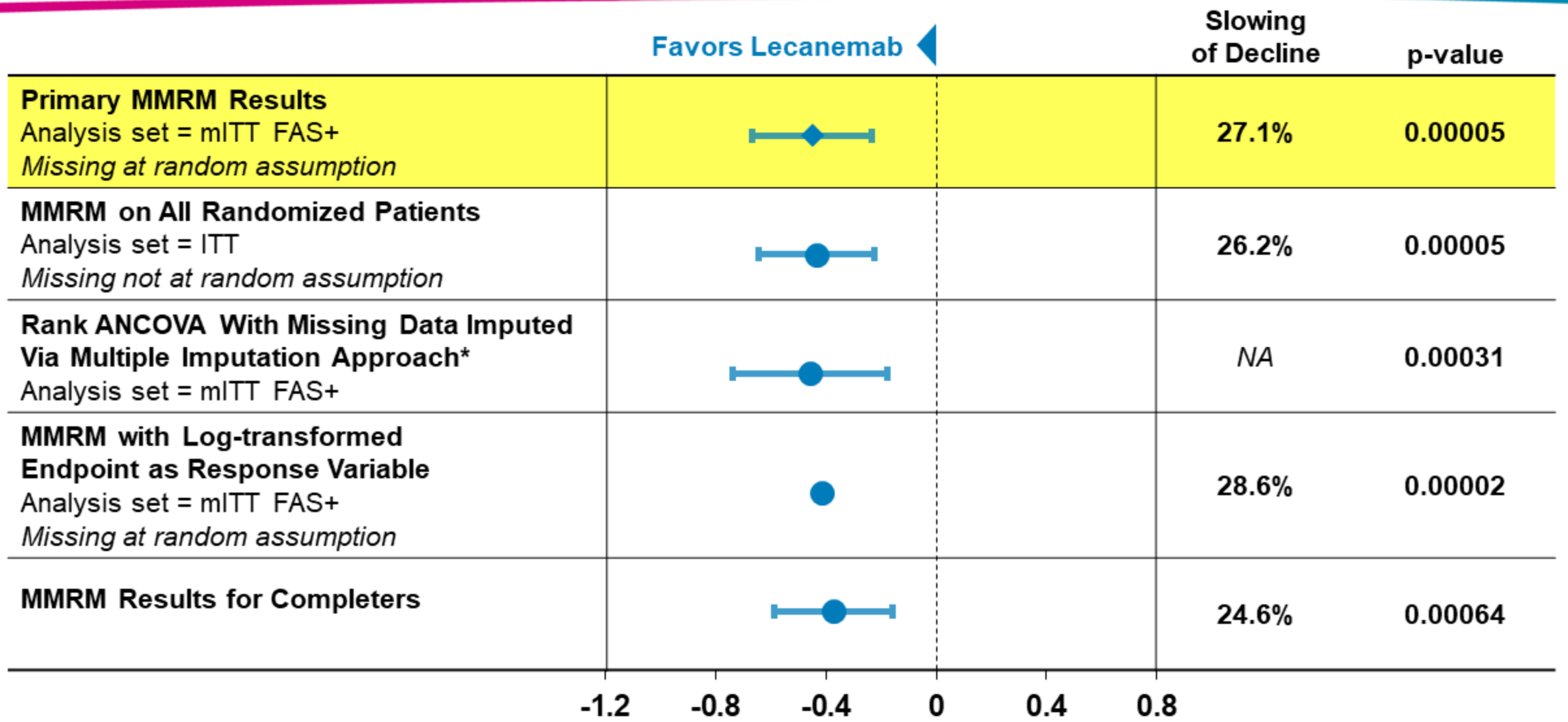
Shobha Dhadda, PhD

Senior Vice President
Global Head, Biostatistics and Clinical Development Operations
Alzheimer's Disease and Brain Health
Eisai Inc.

All Analyses Consistently Show Highly Statistically Significant Results

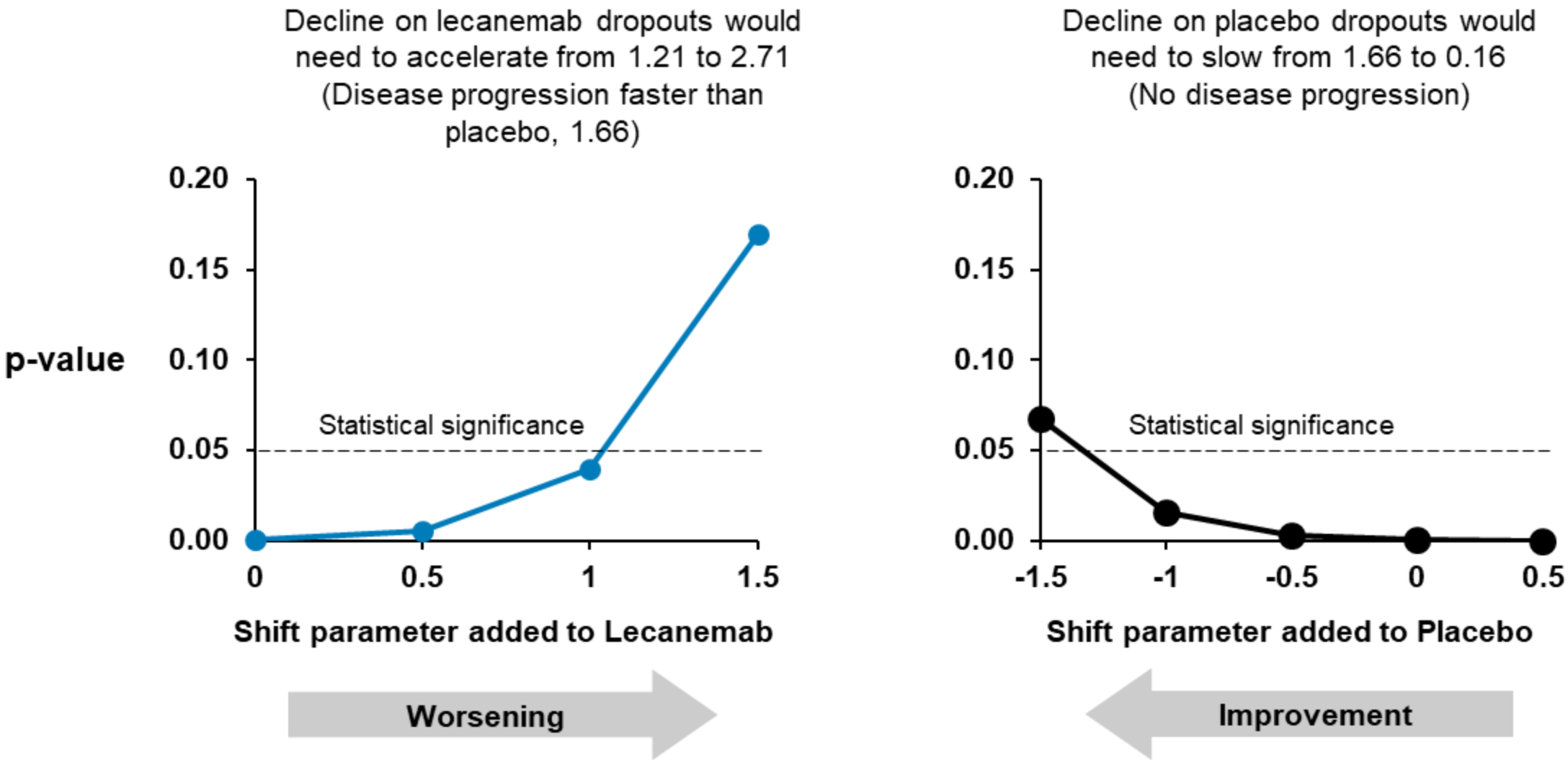
- Robustness demonstrated using:
  - Sensitivity analyses using various statistical methods to assess impact of different assumptions on missing data
  - Analyses to assess impact of intercurrent events (discontinuations, use of symptomatic AD medications)
  - Analyses to assess impact of Amyloid-Related Imaging Abnormalities (ARIA) and infusion-related reaction
  - Subgroup analyses by randomization strata

Study 301: Sensitivity Analyses Confirm Robustness of CDR-SB Primary Endpoint via Different Statistical Methods

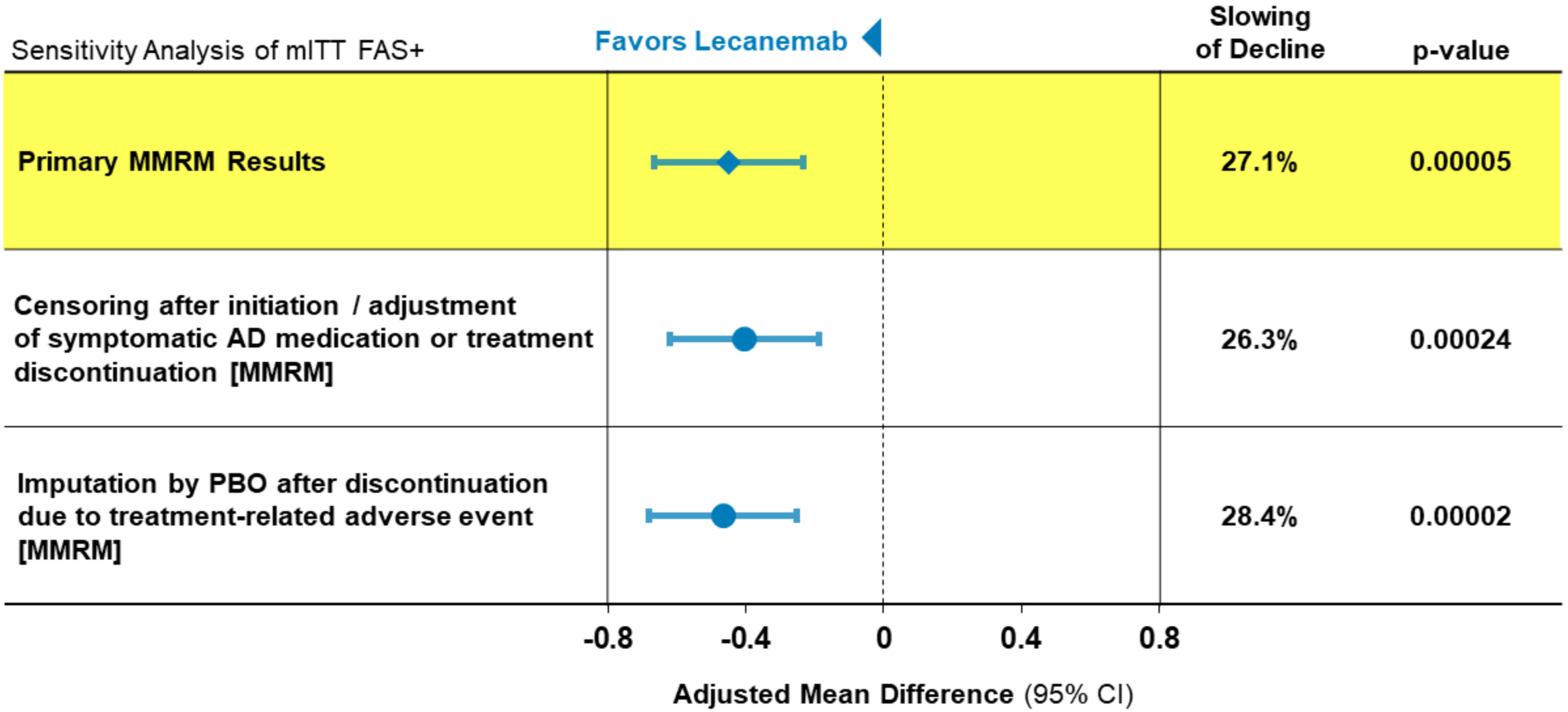


*Hodges-Lehmann non-parametric estimate of median difference
MMRM = mixed model for repeated measures

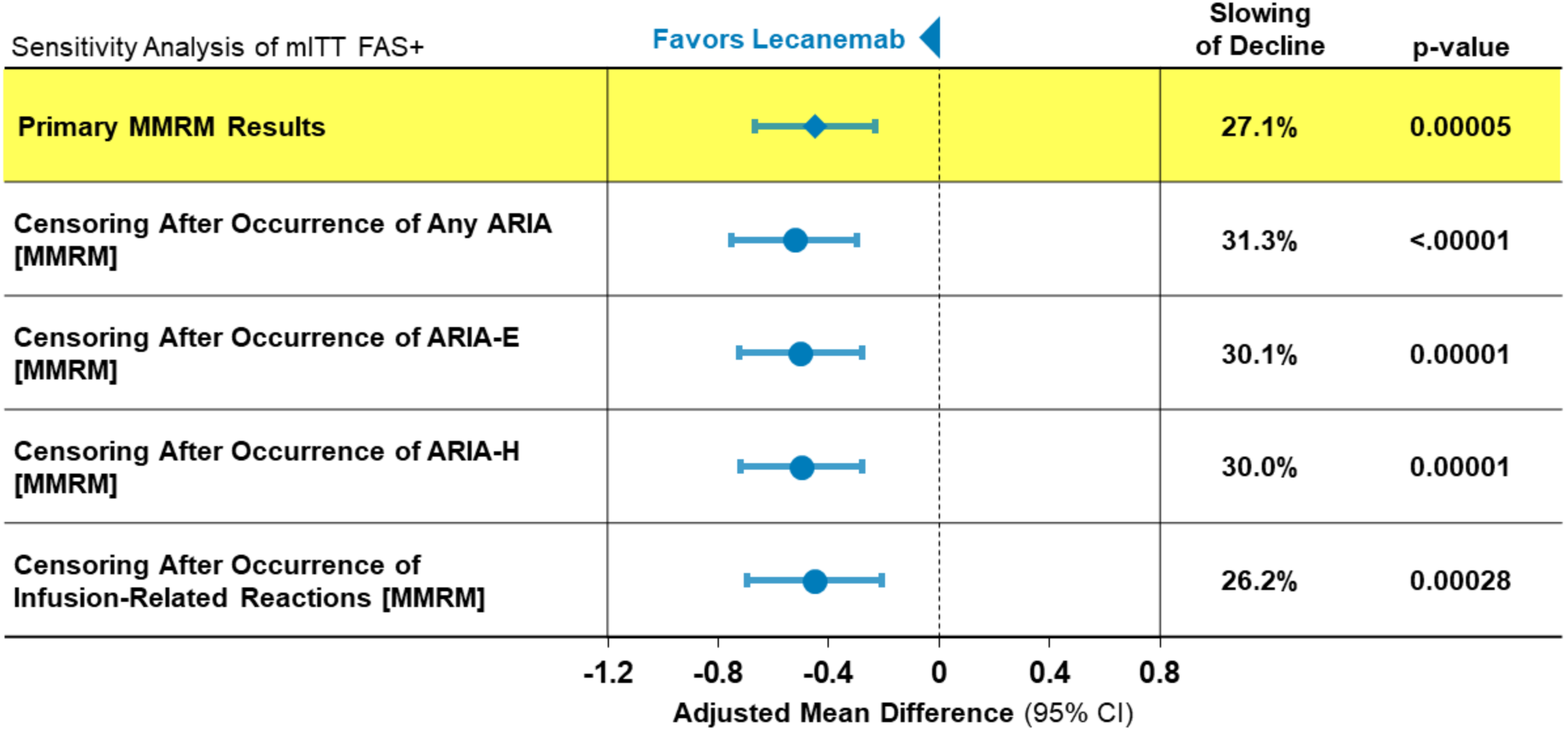
Study 301: Pre-specified CDR-SB Tipping Point Analysis Strongly Reinforces Primary Analysis Results



Study 301: Analyses of Intercurrent Events Confirm Robustness of CDR-SB Primary Endpoint



Study 301: Analyses for Potential Unblinding by ARIA or Infusion-Related Reactions Support Robust Effect

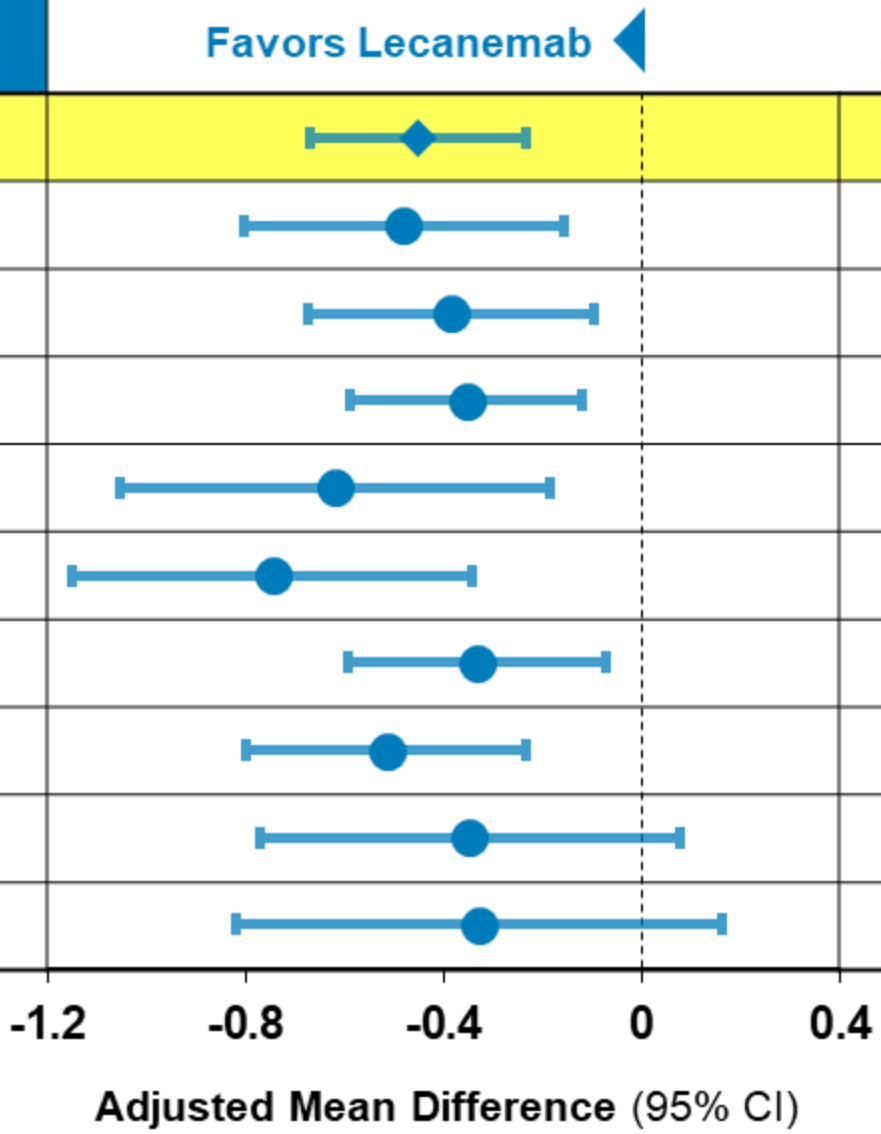


Efficacy Results by Randomization Strata

- Symptomatic AD medication at Baseline (Yes / No)
- Clinical subgroup (MCI or mild AD)
- *APOE4* status (Carrier / Noncarrier)
- Region

Study 301: Consistent CDR-SB Results Across Subgroups

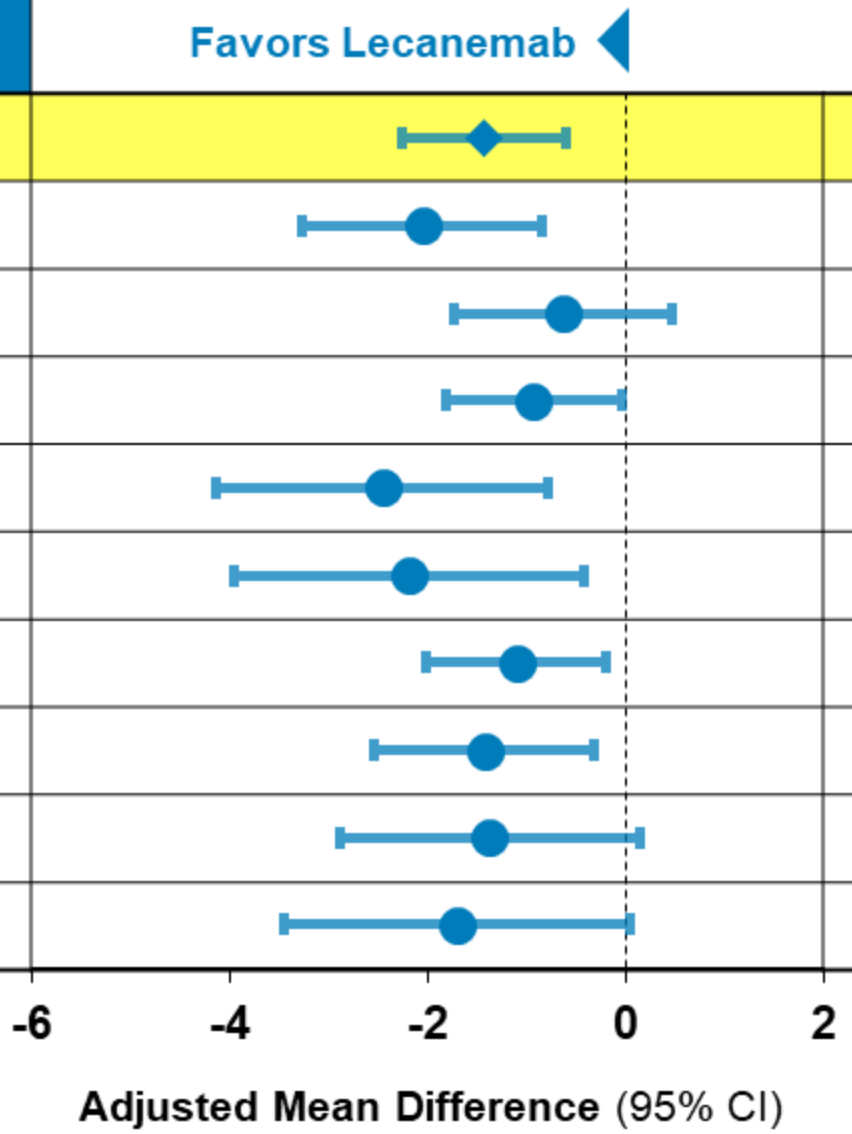
		PBO (N)	LEC (N)	Slowing of Decline
Overall		875	859	27%
Symptomatic AD Meds at Baseline	Yes	468	447	25%
	No	407	412	28%
Clinical Subgroup	MCI	544	528	28%
	Mild AD	331	331	27%
APOE4 Status	Noncarrier	275	267	41%
	Carrier	600	592	21%
Region	North America	516	514	34%
	Asia	146	141	25%
	Europe	213	204	14%



Values rounded

Study 301: Consistent ADAS-Cog14 Results Across Subgroups

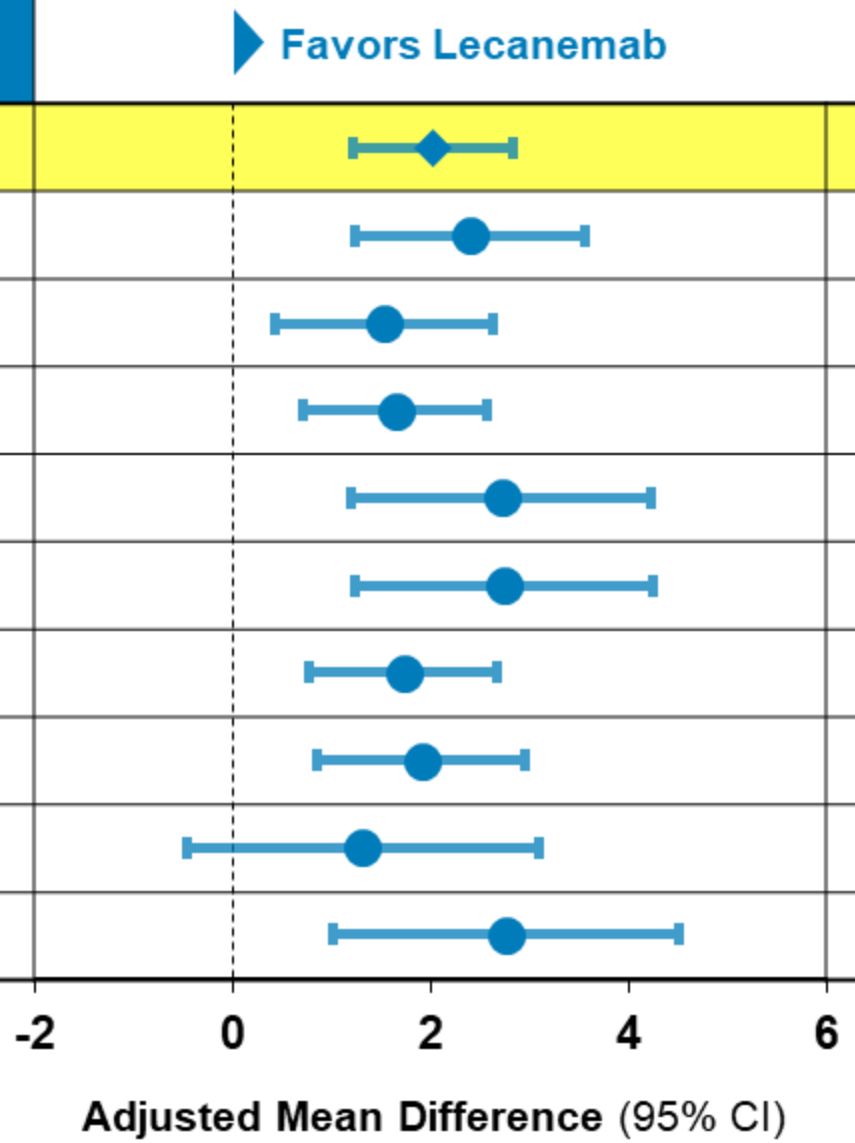
		PBO (N)	LEC (N)	Slowing of Decline
Overall		872	854	26%
Symptomatic AD Meds at Baseline	Yes	466	445	29%
	No	406	409	16%
Clinical Subgroup	MCI	542	525	23%
	Mild AD	330	329	30%
APOE4 Status	Noncarrier	273	266	35%
	Carrier	599	588	21%
Region	North America	514	512	31%
	Asia	146	140	25%
	Europe	212	202	22%



Values rounded

Study 301: Consistent ADCS MCI-ADL Results Across Subgroups

		PBO (N)	LEC (N)	Slowing of Decline
Overall		**796**	**783**	**37%**
Symptomatic AD Meds at Baseline	Yes	423	404	37%
	No	373	379	33%
Clinical Subgroup	MCI	499	492	38%
	Mild AD	297	291	38%
APOE4 Status	Noncarrier	245	234	47%
	Carrier	551	549	33%
Region	North America	473	473	42%
	Asia	130	121	23%
	Europe	193	189	41%



Values rounded

Study 301 Met All Primary and Key Secondary Endpoints, Consistent with Slowing of Disease Progression

- Highly significant results for CDR-SB, ADAS-Cog14, ADCS MCI-ADL
  - $p < 0.011$ at 6 months for all
  - $p < 0.001$ at 18 months
- Meaningful slowing of cognitive and functional decline
  - Results were consistent across endpoints and subgroups
  - Sensitivity analyses confirm robustness of results
  - Significant slowing of decline in QoL and care partner burden*
- Significant reduction in amyloid plaques
  - Improvements in biomarkers of amyloid, tau, neurodegeneration, and gliosis provide biological basis for treatment effects

*Data presented in briefing document, and discussed later in presentation

Study 301 Safety

Michael Irizarry, MD, MPH

Senior Vice President
Deputy Chief Clinical Officer
Alzheimer's Disease and Brain Health
Eisai Inc.

Study 301: Safety Exposures

Duration	Placebo N = 897	Lecanemab N = 898
Mean (months)	**16.49**	**15.74**
≥ 3 months	**880** (98%)	**841** (94%)
≥ 6 months	**860** (96%)	**816** (91%)
≥ 12 months	**800** (89%)	**765** (85%)
≥ 18 months	**731** (81%)	**698** (78%)

Values rounded

Study 301: Overall Safety Profile

	Placebo N = 897	Lecanemab N = 898
Adverse Event (AE)	82%	89%
Serious Adverse Event (SAE)	11%	14%
Infusion-Related Reaction SAE	0	1.2%
ARIA-E SAE	0	0.8%
ARIA-H SAE	0.1%	0.6%
AEs Leading to Study Drug Withdrawal	3%	7%
Deaths*	7 (0.8%)	6 (0.7%)

*There were 2 additional deaths that occurred > 30 days after last study treatment administration (placebo 1, lecanemab 1)
Values rounded

Study 301: Only ARIA and Infusion-Related Reactions Have Important Difference from Placebo

Most Common AEs	Placebo N = 897	Lecanemab N = 898
Any AE	82%	89%
Infusion-Related Reactions	7%	26%
Amyloid-Related Imaging Abnormalities–Hemorrhage (ARIA-H)	9%	17%
Amyloid-Related Imaging Abnormalities–Edema (ARIA-E)	2%	13%
Headache	8%	11%
Fall	10%	10%
Urinary Tract Infection	9%	9%
COVID-19	7%	7%
Back Pain	6%	7%
Arthralgia	7%	6%
Diarrhea	6%	5%
Dizziness	5%	5%
Anxiety	4%	5%

No important changes in Labs, ECG, Vitals

Values rounded; ECG = electrocardiogram

Adverse Events of Special Interest

- Infusion-Related Reactions
- Amyloid-Related Imaging Abnormalities (ARIA)

Study 301: 96% of Infusion-Related Reactions Were Lower Grades and Usually Occurred Once Early in Treatment

	Placebo N = 897	Lecanemab N = 898
Infusion-Related Reaction	7%	26%
Grade 1	5%	9%
Grade 2	3%	17%
Grade 3	0	6 (0.7%)
Grade 4	0	1 (0.1%)

- 75% of events occurred with first dose
  - 6 of 7 Grade 3 or 4 reactions occurred on the first dose
- 66% of patients with Infusion-Related Reaction had single events

Values rounded; 3 patients on lecanemab have missing in CTCAE Grade

Amyloid-Related Imaging Abnormalities are Identified by MRI and Generally Asymptomatic

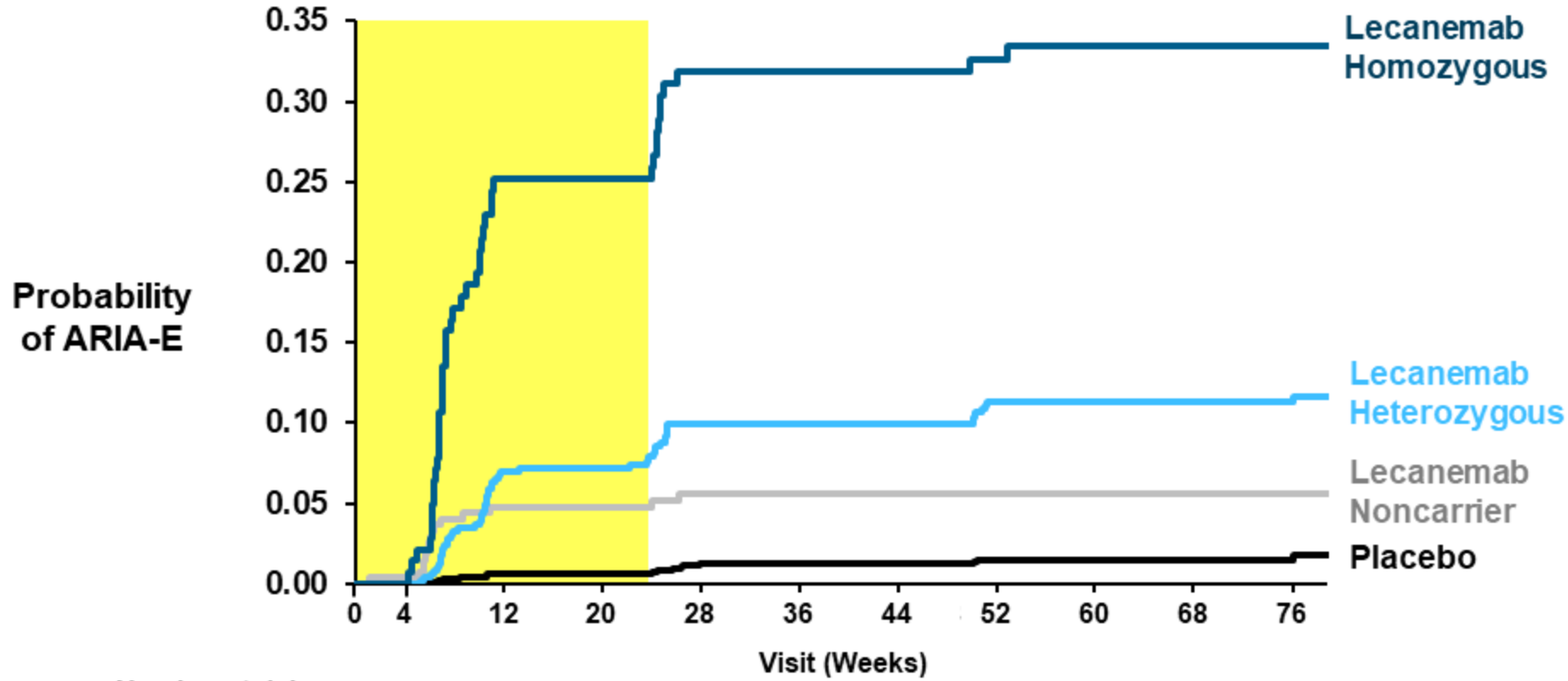
ARIA-Edema (ARIA-E)	ARIA-Hemorrhages (ARIA-H)
Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities	Micro- or macro-hemorrhages observed as hypointense hemosiderin deposition in parenchyma or leptomeningeal/subpial space (superficial siderosis)

- ARIA is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA])
- CAA is present pathologically in almost all AD cases, but most patients show no imaging findings (microhemorrhage) or clinical manifestations (intracerebral hemorrhage or inflammatory CAA)
- There is an increased risk of ARIA with monoclonal antibodies that remove amyloid
- There is a lack of definitive clinical criteria for diagnosing CAA

Study 301: ARIA-E Events

	Placebo N = 897		Lecanemab N = 898	
ARIA-E	15	**1.7%**	113	**12.6%**
ARIA-E by *APOE4* genotype				
Noncarrier	1/286	**0.3%**	15/278	**5.4%**
Carrier	14/611	**2.3%**	98/620	**15.8%**
Heterozygous	9/478	**1.9%**	52/479	**10.9%**
Homozygous	5/133	**3.8%**	46/141	**32.6%**
Symptomatic ARIA-E	0	**0**	25	**2.8%**
Noncarrier	0	**0**	4/278	**1.4%**
Carrier	0	**0**	21/620	**3.4%**
Heterozygous	0	**0**	8/479	**1.7%**
Homozygous	0	**0**	13/141	**9.2%**

Study 301: ~90% of ARIA-E Cases Occurred ≤ 6 Months of Treatment, Resolved Within 4 Months of Detection



Number at risk:

Lecanemab Homozygous (N)	141	101	100	91	89	89	88	86	85	83
Lecanemab Heterozygous (N)	479	423	410	395	387	381	374	367	362	343
Lecanemab Noncarrier (N)	277	255	247	239	231	221	216	211	205	204
Placebo (N)	897	879	863	850	822	800	792	777	762	731

MRI at Screening, 9 weeks, 13 weeks, 6 months, 12 months and 18 months

Study 301: Isolated ARIA-H (Without ARIA-E) Occurred at Similar Rate Between Lecanemab and Placebo

	Total ARIA-H				Isolated ARIA-H (No ARIA-E)			
	Placebo N = 897		Lecanemab N = 898		Placebo N = 897		Lecanemab N = 898	
ARIA-H	81	**9.0%**	155	**17.3%**	70	**7.8%**	80	**8.9%**
***APOE4* Genotype**								
Noncarrier	12/286	**4.2%**	33/278	**11.9%**	11/286	**3.8%**	23/278	**8.3%**
Carrier	69/611	**11.3%**	122/620	**19.7%**	59/611	**9.7%**	57/620	**9.2%**
Heterozygous	41/478	**8.6%**	67/479	**14.0%**	35/478	**7.3%**	40/479	**8.4%**
Homozygous	28/133	**21.1%**	55/141	**39.0%**	24/133	**18.0%**	17/141	**12.1%**
Symptomatic ARIA-H	2	**0.2%**	13	**1.4%**	2	**0.2%**	4	**0.4%**

Study 301: Most ARIA-H Events Were Microhemorrhages and Superficial Siderosis in Conjunction with ARIA-E

	Total ARIA-H				Isolated ARIA-H (No ARIA-E)			
	Placebo N = 897		Lecanemab N = 898		Placebo N = 897		Lecanemab N = 898	
ARIA-H	81	**9.0%**	155	**17.3%**	70	**7.8%**	80	**8.9%**
Microhemorrhage	68	**7.6%**	126	**14.0%**	63	**7.0%**	60	**6.7%**
Superficial siderosis	21	**2.3%**	50	**5.6%**	13	**1.4%**	23	**2.6%**
Intracerebral hemorrhage (> 1cm)*	2	**0.2%**	6	**0.7%**	1	**0.1%**	4	**0.4%**

*Includes 2 patients with intracerebral hemorrhage that occurred > 30 days after last study treatment administration (placebo 1, lecanemab 1)

Study 301: Rates of ARIA Not Increased with Concurrent Antiplatelet or Anticoagulant Use Relative to Lecanemab Alone

	ARIA-E		ARIA-H (microhemorrhage or superficial siderosis)		Intracerebral Hemorrhage	
	Placebo	Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab
No Antiplatelet or Anticoagulation at Any Time	9/584 **(1.5%)**	74/545 **(13.6%)**	49/584 **(8.4%)**	93/545 **(17.1%)**	1/584 **(0.2%)***	3/545 **(0.6%)**
Event Post Any Antiplatelet (aspirin or non-aspirin)	2/243 **(0.8%)**	30/271 **(11.1%)**	22/243 **(9.1%)**	44/271 **(16.2%)**	1/243 **(0.4%)**	1/271 **(0.4%)**
Event Post Any Anticoagulation (alone or with antiplatelet)	2/72 **(2.8%)**	4/79 **(5.1%)**	7/72 **(9.7%)**	11/79 **(13.9%)**	0/72 **(0%)**	2/79 **(2.5%)***

*Includes one case on placebo and one case on lecanemab with ICH > 30 days after discontinuing study medication

Lecanemab was Well-Tolerated in Elderly Population With Comorbidities and Concomitant Medications

- Lecanemab was generally well-tolerated
  - Comparable to placebo with exception of ARIA and Infusion-Related Reaction
- ARIA and Infusion-Related Reaction generally occurred early in treatment
  - Supports monitoring during first 6 months
- Follow USPI for ARIA monitoring

USPI = United States Prescribing Information

Clinician's Perspective

Sharon Cohen, MD, FRCPC

Medical Director and
Site Principal Investigator
Toronto Memory Program

Treatment Goals to Address Urgent Unmet Need in Alzheimer's Disease

- Improving/maintaining core abilities of
  - Cognition
  - Daily function
  - Behavior
- Slowing disease progression to remain at less debilitating and less costly stages of disease
- Maintaining quality of life for patients and care partners
- Intervening early in the disease when abilities and quality of life are still acceptable

Clinical Dementia Rating Scale (CDR)

CDR Yields 2 Scores

- Global CDR Score - stages disease
- CDR-SB - discerns change over time

CDR Domains

- Memory
- Orientation
- Judgment and problem solving
- Community affairs
- Home and hobbies
- Personal care

Rating Scale for Each Domain

None = 0	Questionable / Slight = 0.5	Mild / Unable to Function Independently = 1	Moderate = 2	Severe = 3

Full CDR-SB range: 0-18; in MCI or Mild AD typical range: 0.5 to 6

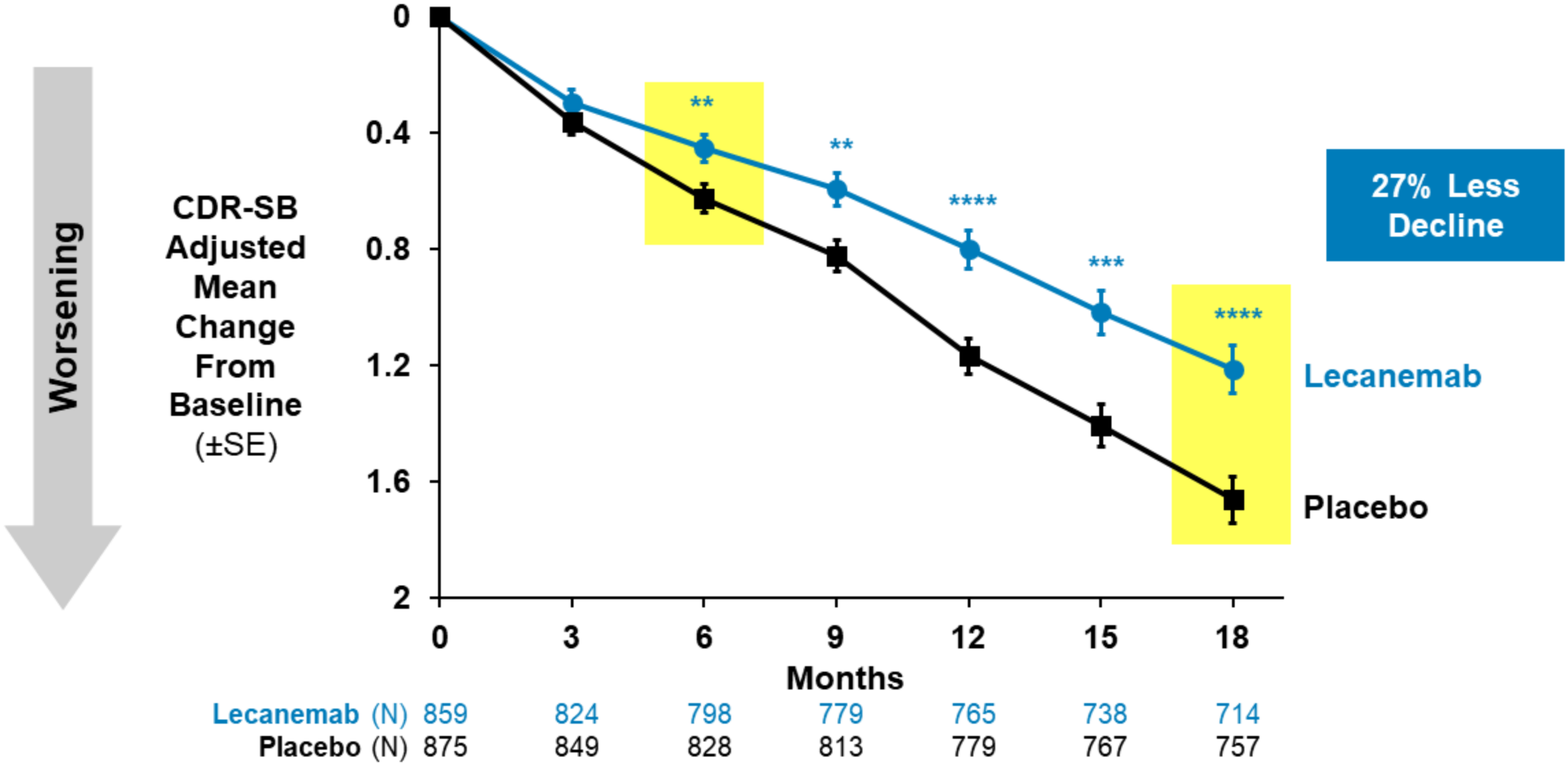
- Moving from 0 to 0.5 ≈ progressing from unimpaired to impaired
- Moving from 0.5 to 1 ≈ progressing from slight impairment to loss of independence

Slowing of Decline on CDR-SB is Clinically Meaningful in Patients With MCI and Mild AD

- Literature and AD experts consider 20-30% slowing of disease as clinically meaningful[1,2]
- CDR incorporates input from expert clinicians, patients, and care partners and measures outcomes meaningful to patients and care partners
- Clinically meaningful effect can be established by demonstration of benefit on core cognitive and functional symptoms of AD on CDR-SB at treatment group level
- Benefits may be expected to increase over time on CDR-SB with treatment that impacts underlying pathophysiology of AD
- CDR-SB can also demonstrate saving of time at earlier stage of AD

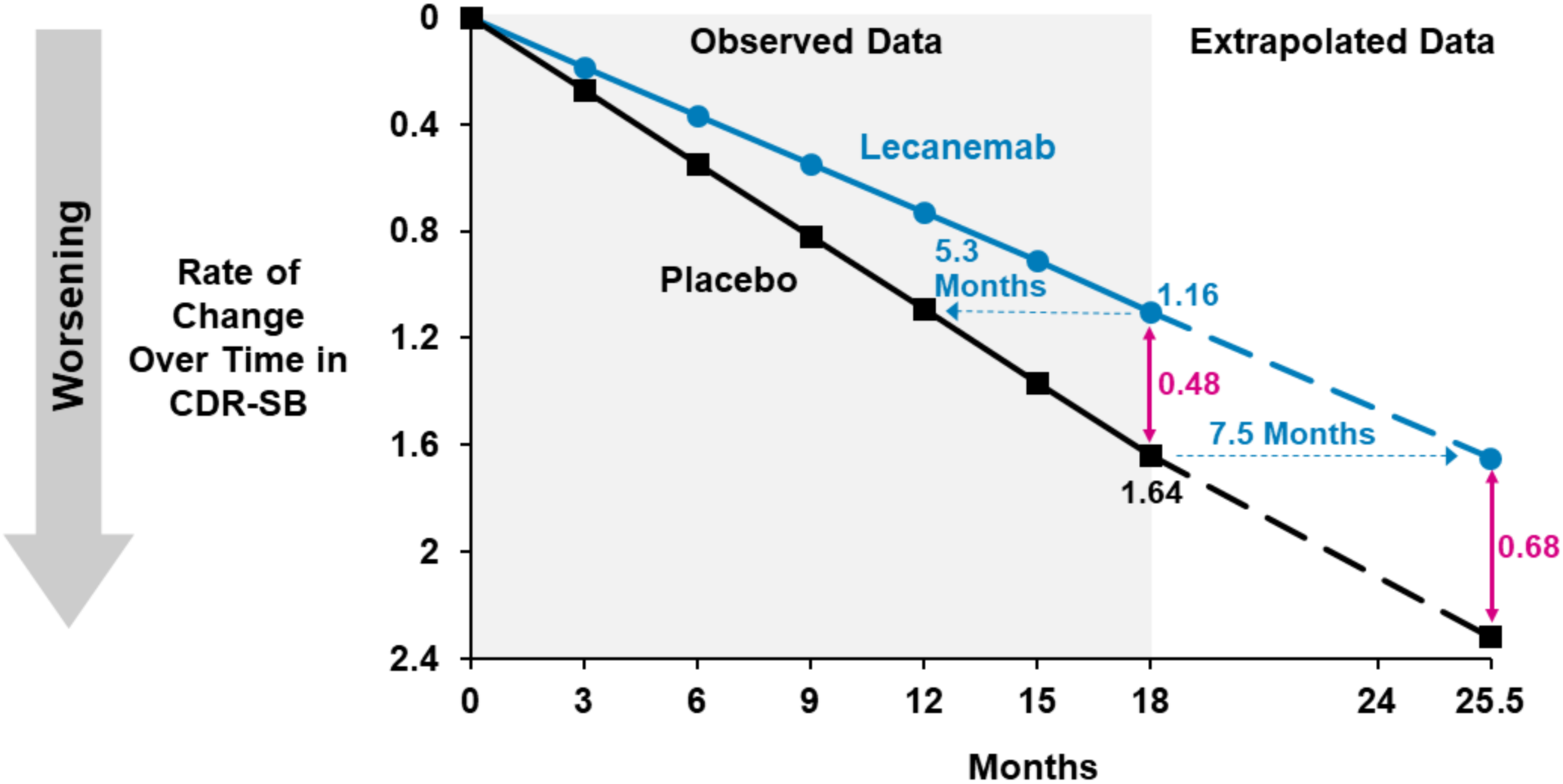
1. Abushakra, et al., 2016; 2. Petersen, et al., 2023

Lecanemab Significantly Slowed Disease Progression



**p < 0.01; ***p < 0.001; ****p < 0.0001

Lecanemab-Treated Patients Maintained at Earlier Stages of Disease for Longer (Slope Analysis Using CDR-SB)

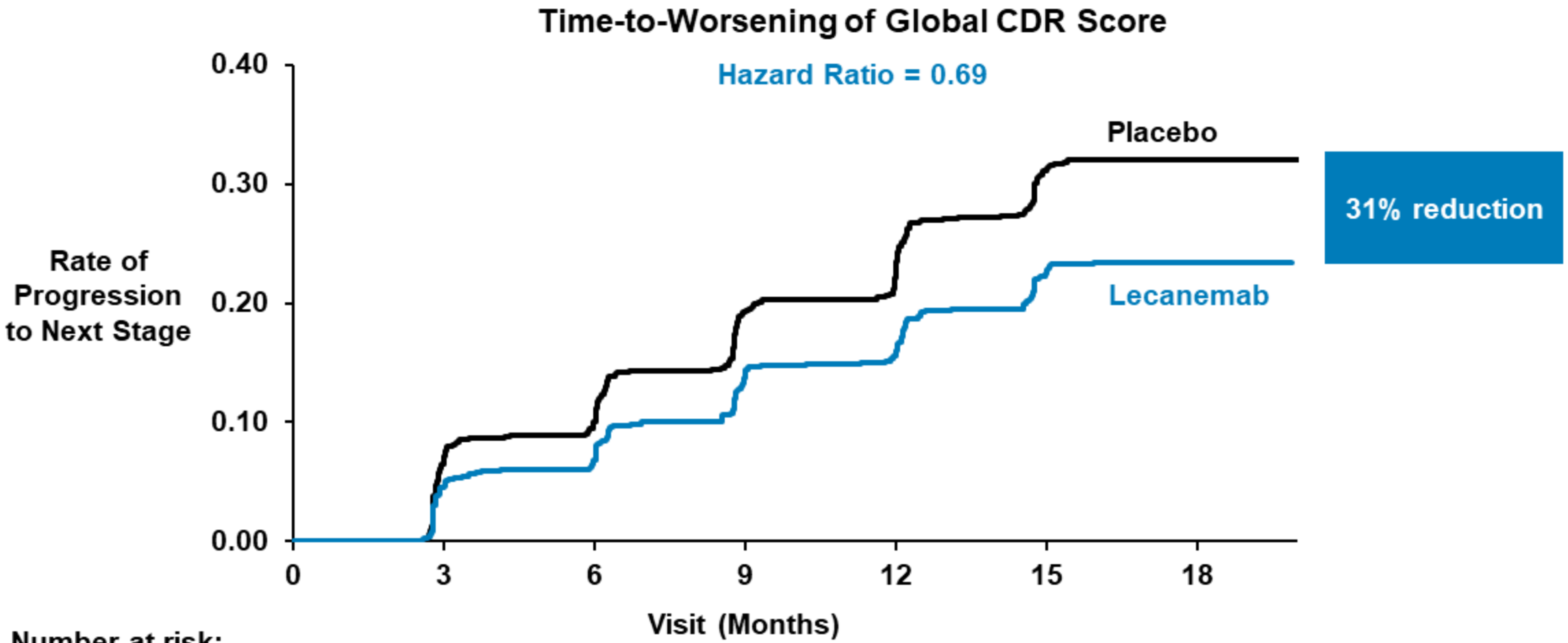


Note: Rate of change over time (mean slope) based on change from baseline in CDR-SB analyzed using linear mixed effects (LME) model; LME model included time, treatment by assessment time as covariate with random intercept and slope

Vital to Remain at Earlier Disease Stages, Avoiding Progression to Landmark Events

- Loss of independence is a landmark event
- Progression from MCI to mild dementia means that one is no longer independent in one or more activities
  - May be unable to work, drive, bank, travel, live alone, pursue hobbies
- Progression from mild dementia to moderate dementia translates into more substantial losses of autonomy across multiple activities
  - Many tasks abandoned; greater need for supervision
  - May need hands on assistance for basic personal care activities such as dressing, toileting, bathing

Study 301 Showed that Patients Treated With Lecanemab had Meaningful Delay in Time-to-Worsening



Number at risk:

Lecanemab (N)	859	801	765	677	642	554	299
Placebo (N)	875	792	757	649	603	524	265

Progression was defined as Global CDR Score progressing from 0.5 [MCI] to 1 [mild AD dementia] or 1 [mild dementia] to 2 [moderate dementia]

Health-Related Quality of Life

- Perception of how one's well-being is affected by a disease, disability, or disorder
- Not interchangeable with health status
- Broader than activities of daily living but often correlates with function
- Ideally rated by patients in relation to their personal expectations, which can vary over time and with disease
- Questionnaires may be multidimensional, covering physical, social, emotional, cognitive, work/role-related and/or disease-related
- Provides patient-reported outcomes which are central to understanding value of treatment

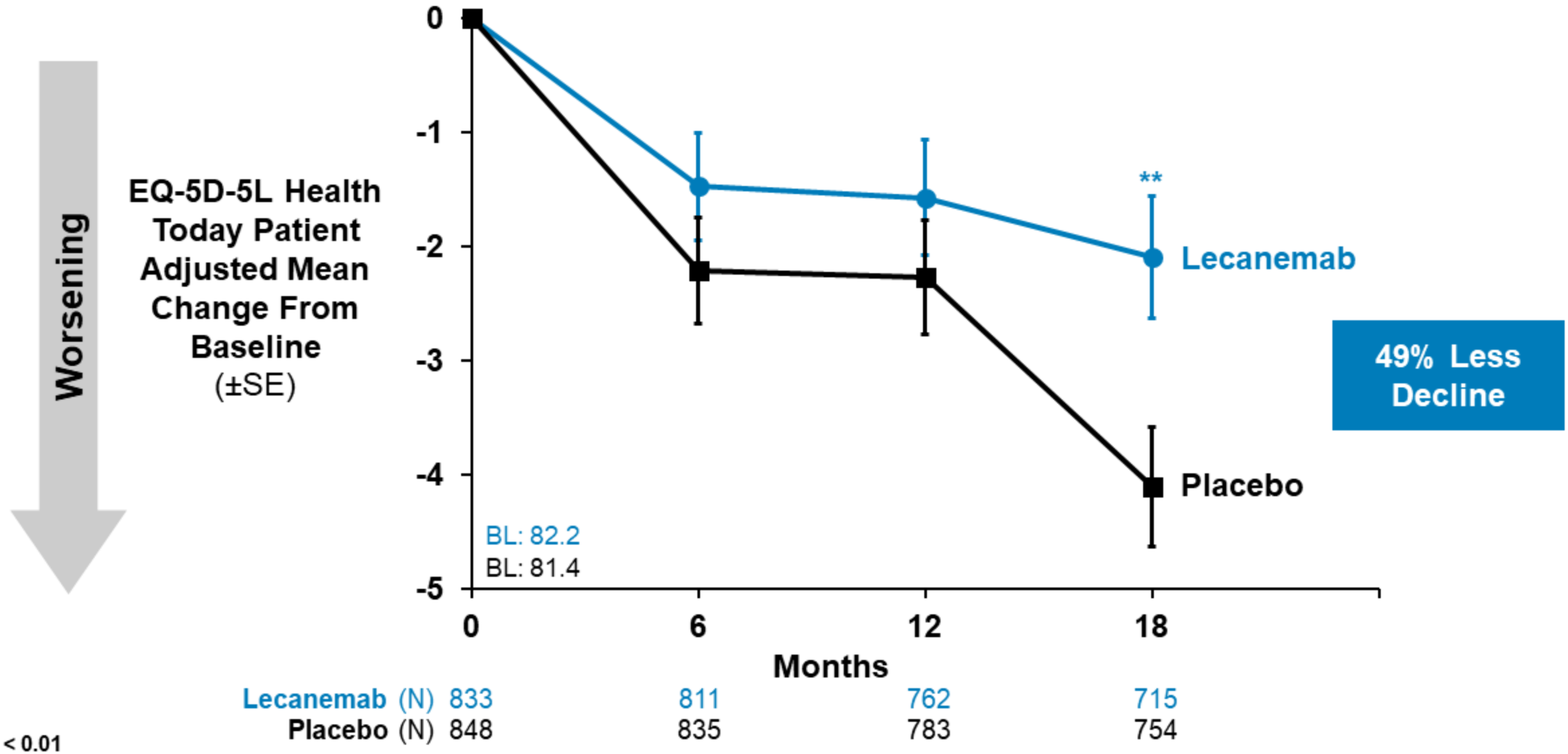
Summary of Health-Related Quality of Life Assessments

Tool	Evaluation	Scale	Source of Input	Total Score Range	Assessments
European QOL-5 Dimensions (EQ-5D-5L)	5 Health Dimensions (Self-care, Usual Activities, Anxiety/Depression, Mobility*, Pain/Discomfort*)	5 dimensions, each with 5 levels of severity	Patient	0 (worst) to 100 (best)	Baseline; every 6 months
Quality of Life in AD (QOL-AD)	Quality of life of patient with AD	13-item questionnaire, each with 4 levels of severity	Patient	13 (worst) to 52 (best)	Baseline; every 6 months
Zarit Burden Interview	Stresses experienced by care partners of patients with dementia	22-item instrument, each with 5 levels of severity	Care partner	0 (best) to 88 (worst)	Baseline; every 6 months

In MCI and mild AD, patients themselves are most appropriate source of QoL information, while care partners are most appropriate source for care partner burden

*Not applicable to patients with MCI or mild AD

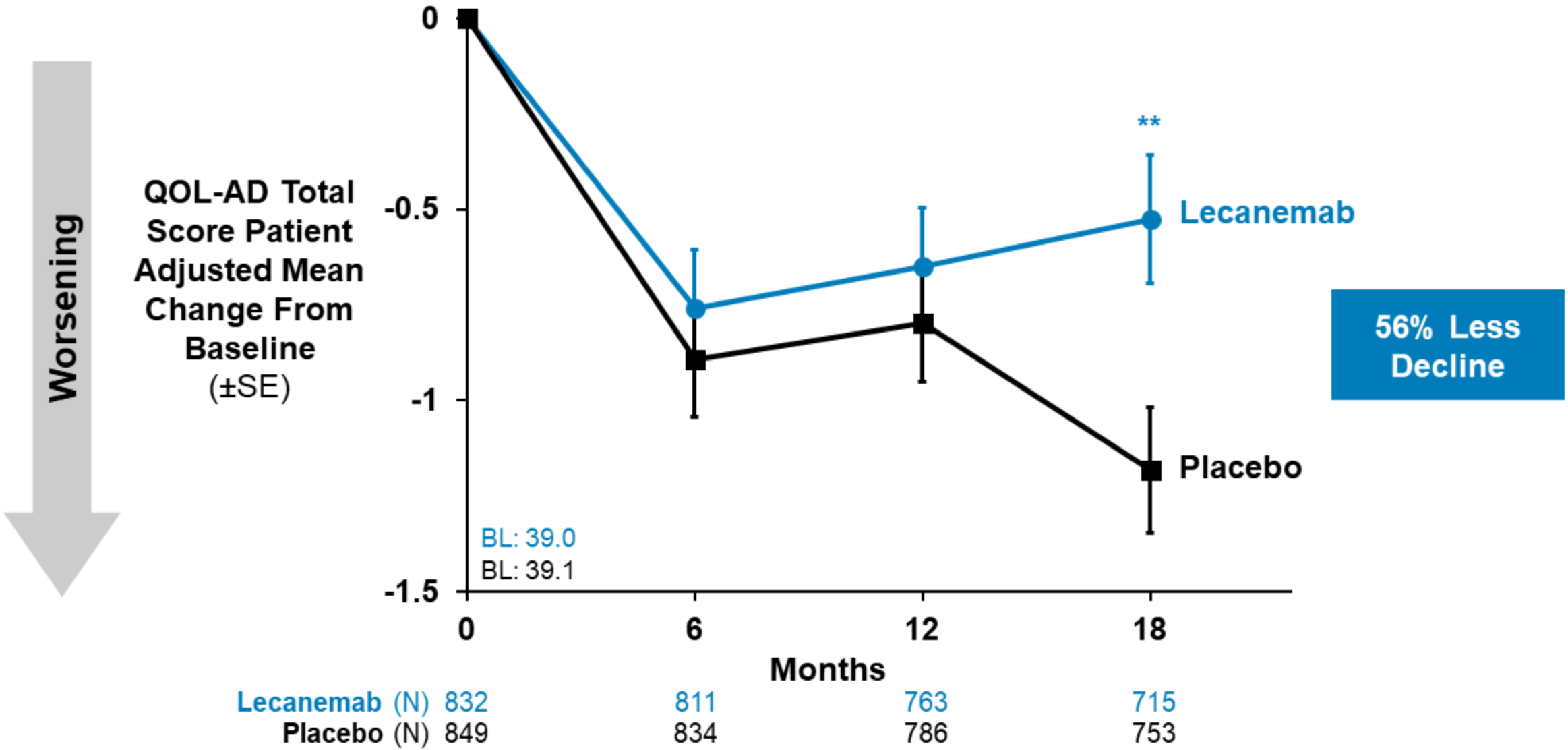
EQ-5D-5L* (Health Today Rated by Patient): Patients Had 49% Less Decline



**p < 0.01

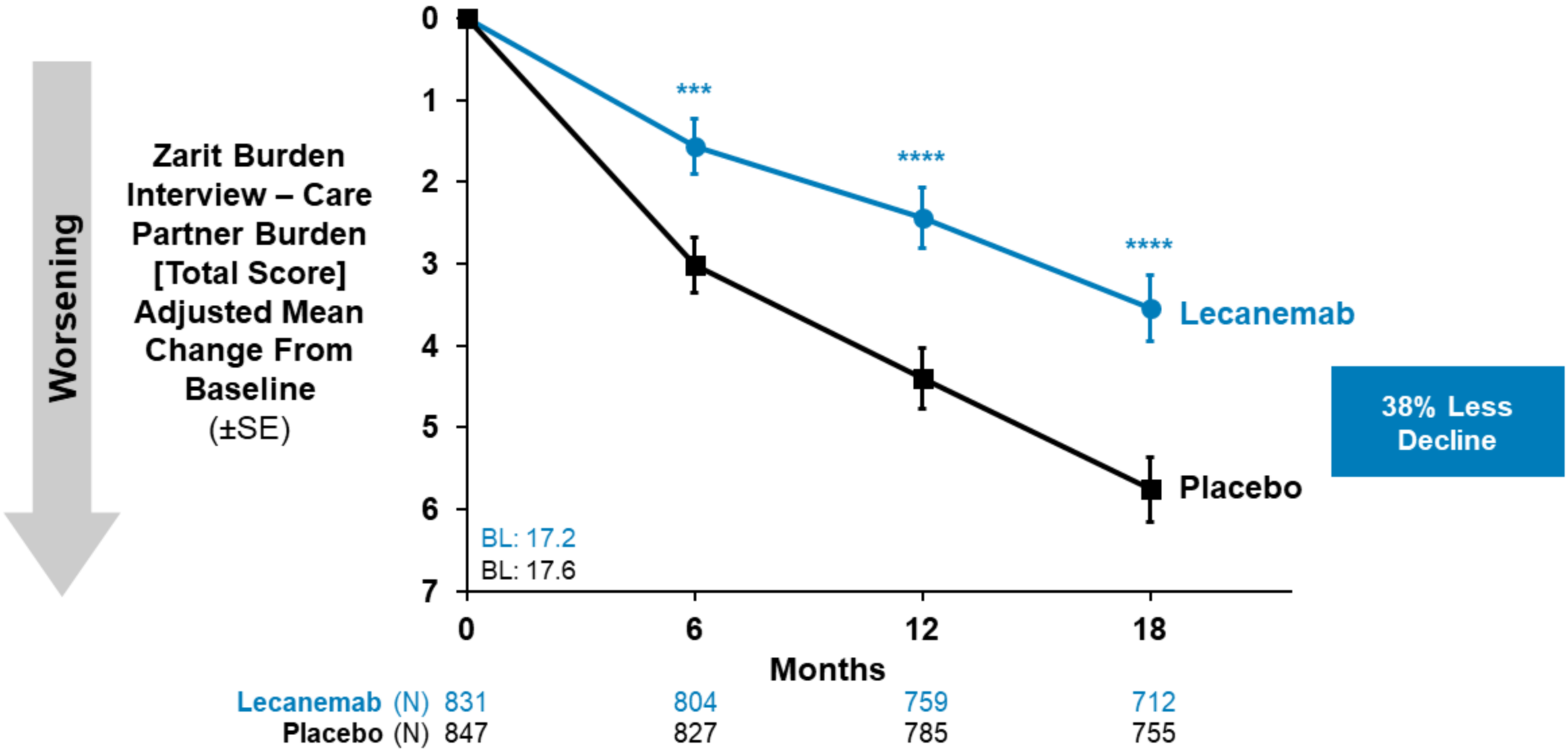
*Most relevant dimensions to early AD are self-care, usual activities, anxiety/ depression

QOL-AD (Rated by Patient): Patients Had 56% Less Decline



**p < 0.01

Zarit Burden Interview: Care Partner Burden Reduced by 38%



****p < 0.0001

Lecanemab Provides Clinically Meaningful Benefits to Patients and Care Partners: A Clinician's Perspective

- Clinicians value consistent data across multiple key aspects of disease being treated and the opportunity to intervene early
  - 26-37% slowing of disease progression on clinical scales
  - 38-56% less decline in health-related quality of life
- Patients and clinicians value disease slowing at the earliest clinical stages in an otherwise relentlessly progressive, disabling disease
- Diverse study population, with respect to age, background medications, comorbidities, and race, provide treating physicians with confidence that study results will be applicable to real-world patients
- QoL measures are rarely reported in AD studies; positive QoL results over multiple scales provide patient centricity that is of paramount importance to clinicians striving to meet needs of their patients

Conclusion

Lynn Kramer, MD, FAAN

Chief Clinical Officer

Alzheimer's Disease and Brain Health

Eisai Inc.

Lecanemab: Confirmatory Study 301 Demonstrated Consistent, Persistent, Slowing of Disease Progression in Patients With Early AD

Selectively targets amyloid beta (Aβ) protofibrils

Highly statistically significant and clinically meaningful slowing in multiple measures of clinical decline, and effects on biomarkers consistent with slowing of disease progression

Well-tolerated with well-characterized safety, supporting a positive benefit-risk profile

Conducted in patients with broad range of comorbidities and concomitant medications from a diverse racial and ethnic background, clinical trial practice settings generalizable to US population

Study 301: The Confirmatory Study to Verify and Describe the Clinical Benefit of Lecanemab for the Treatment of Early AD

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

Eisai Inc.

June 9, 2023

Backup Slides Shown

ARIA-E and -H: Guidance for Patients and Care Partners in Current Medication Guide

MEDICATION GUIDE
LEQEMBI™ (leh-kem'-bee)
(lecanemab-irmb)
injection, for intravenous use

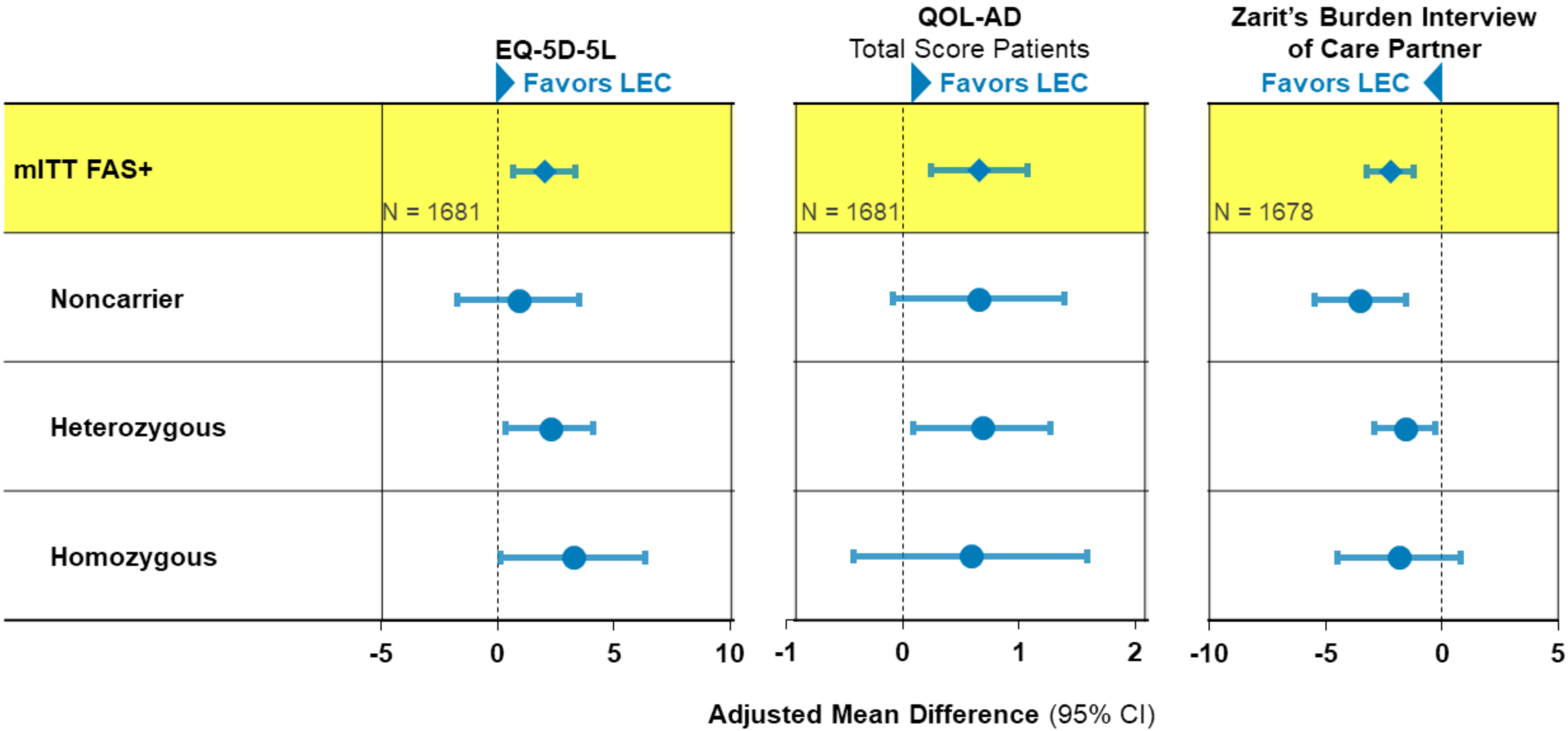
What is the most important information I should know about LEQEMBI?
LEQEMBI can cause serious side effects including:

- **Amyloid Related Imaging Abnormalities or "ARIA". ARIA is a side effect that does not usually cause any symptoms but serious symptoms can occur.** ARIA is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain, and infrequently, larger areas of bleeding in the brain can occur. Most people with this type of swelling in the brain do not get symptoms, however some people may have symptoms, such as:
  - headache
  - confusion
  - dizziness
  - vision changes
  - nausea
  - difficulty walking
  - seizures

Your healthcare provider will do magnetic resonance imaging (MRI) scans before and during your treatment with LEQEMBI to check you for ARIA. Some people have a genetic risk factor (homozygous apolipoprotein E gene carriers) that may cause an increased risk for ARIA. Talk to your healthcare provider about testing to see if you have this risk factor.

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

Study 301: Homozygous *APOE4* Carriers Improved on QOL Outcomes Similar to Overall Population



Study 301: CDR-SB By Concomitant Medication