Lifetime Clinical Benefits of Lecanemab in Early Alzheimer's Disease Using Simulation Modeling

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Introduction

- Alzheimer's disease (AD), the most common cause of dementia and leading cause of death among older populations in the US, exerts a significant burden on patients and their caregivers[1, 2]
- Lecanemab is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated AB species (protofibrils) with activity at insoluble fibrils
- Study 201 trial was a randomized, double-blind, phase II study using a Bayesian adaptive design with response adaptive randomization to assess the efficacy and safety of lecanemab vs. placebo in 856 patients with mild cognitive impairment (MCI) due to AD and mild AD dementia (Study 201; NCT01767311)[3]
- Statistical significance was achieved on key endpoints evaluating efficacy after 18 months of treatment in patients receiving the highest treatment dose (10 mg/kg biweekly) vs placebo[4]
- This included reduction of amyloid by PET standard uptake value ratio (SUVr) accumulated in the brain (-0.30 adjusted mean change from baseline) and slowing cognitive decline measured with ADCOMS by 30%, Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) by 26%, and AD assessment scale cognitive subscale 14 by 47%[4]

Objectives

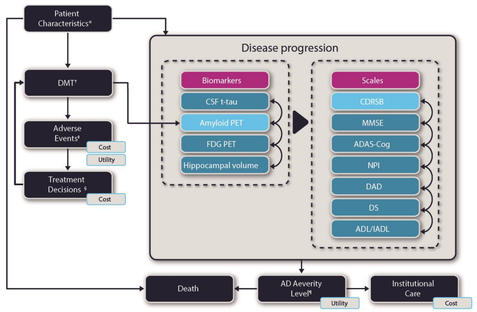
- The objective of this study was to assess long-term health outcomes of lecanemab for patients with early AD (MCI due to AD and mild AD dementia) using a patient-level simulation model
- The modeled base case explored the early AD population of MCI due to AD and mild AD dementia and confirmed Aβ pathology
- Assessments were also conducted in key patient subsets: MCI due to AD; mild AD dementia; and younger MCI due to AD population (with a mean age of 65 years)

Methods

Model Overview and Structure

- The AD ACE model is a patient-level simulator that captures the pathophysiology and management of AD, focusing on the effects of disease modification and early intervention on disease progression[5, 6]
- Disease progression is simulated based on changes in the underlying biomarkers (e.g., measures of Aβ and tau levels), and their connections to clinical presentation of AD, which are measured by various patient-level scales of cognition, behavior, function, and dependence (Figure 1)
- Relationships among changes in these measures over time are quantified using predictive mixed linear equations derived from observational data from the AD Neuroimaging Initiative (ADNI)[7]

Figure 1. Model Diagram



* Key baseline patient characteristics: age, sex, race, education, Apoε4 status, baseline biomarkers, baseline scales. † DMT effect is directly applied on amyloid PET SUVr level. ‡ Includes ARIA-E. § DMT initiates on confirmed amyloid positive MCI due to AD or mild AD patients and discontinues once patients progress to moderate AD. ¶ Defined by CDRSB thresholds: MCI due to AD <4.5, mild AD ≥4.5 to <9.5, moderate AD ≥9.5 to <16, severe AD ≥16.
Abbreviations: AD = Alzheimer's disease; DMT = disease-modifying therapy; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive; ADL = activities of daily living; Apoε4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormalities-edema/effusion CDRSB = Clinical Dementia Rating Sum of Boxes; CSF t-tau = cerebrospinal fluid total-tau; DAD = Disability Assessment Scale for Dementia; DS = dependence scale; FDG-PET = fluorodeoxyglucose-positron emission tomography; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory Questionnaire; PET = positron emission tomography; SUVr = standard uptake value ratio.

Methods (*continued*)

Analysis

- The analysis focused on early AD patients with MCI due to AD and mild AD dementia and confirmed Aβ pathology with characteristics similar to the Study 201 trial population (Table 1)

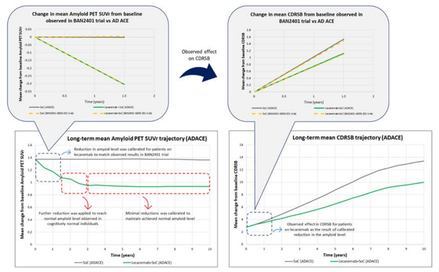
Table 1. Base-case Patient Characteristics and Key Model Inputs

Baseline Characteristic	ADNI Subpopulation	Trial Population (10 mg/kg Biweekly Lecanemab / Placebo)
Base-case: MCI due to AD and mild AD dementia population (with confirmed Aβ pathology)		
Age, median (range), years	71.5 (55–80)	73 (51–88) / 72 (50–89)
PET SUVr, mean (SD)	1.38 (0.14)	1.37 (0.16) / 1.40 (0.16)
MMSE, mean (SD)	25.9 (2.1)	25.6 (2.4) / 26.0 (2.3)
CDR-SB, mean (SD)	2.8 (1.5)	3.0 (1.4) / 2.9 (1.5)
Female, %	46%	42% / 58%
Patient Utilities*	**Values**	**Source**
MCI due to AD	0.80	Landeiro et al., 2020[8]
Mild AD dementia	0.74	
Moderate AD dementia	0.59	
Severe AD dementia	0.36	
Caregiver Disutilities*	**Values**	**Source**
MCI due to AD	0.000	Assumption
Mild AD dementia	0.036	Mesterton et al., 2010[9]
Moderate AD dementia	0.070	
Severe AD dementia	0.086	
Proportion institutionalized, %	**Values**	**Source**
MCI due to AD	0.0%	Assumption
Mild AD dementia	3.8%	Neumann et al., 1999[10]
Moderate AD dementia	11.0%	
Severe AD dementia	25.9%	
HRs for mortality (vs. general population)	**Values**	**Source**
MCI due to AD	1.00	Assumption
Mild AD dementia	2.92	Andersen et al., 2010[11]
Moderate AD dementia	3.85	
Severe AD dementia	9.52	

*Applied both in the community and institutional care settings Abbreviations: Aβ = beta-amyloid; AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CDR SB = Clinical Dementia Rating Sum of Boxes; HR = hazard ratio; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination; PET = positron emission tomography; SD = standard deviation; SUVr = standard uptake value ratio

- A subset of 429 individual patient profiles were selected from the existing 1,735 ADNI patients in the AD ACE simulator that were matched on the key trial inclusion criteria: age range from 50 to 90, Mini-Mental State Examination ≥22, Clinical Dementia Rating (CDR) = 0.5, and amyloid Positron Emission Tomography Standard Uptake Value ratio (PET SUVr) level ≥1.1; 2,000 patients were randomly sampled from this selected subset
- In the AD ACE model, the relationships between biomarkers of disease and clinical outcomes are based on correlations observed in the ADNI data and are incorporated in the model as a set of interconnected equations used to predict disease progression
- Amyloid PET is a predictor in AD ACE disease progression equations; therefore, any calibrated reduction in amyloid PET SUVr at a given time interval impacts the prediction of amyloid PET SUVr and other modeled AD biomarkers and scales (eg, CDR-SB) at later time intervals
- A calibration process to adjust the predicted measures of amyloid PET SUVr at each time interval was used to model the observed treatment effect of lecanemab on CDR-SB over time. The calibration process only adjusted the estimated PET SUVr values over time and did not impact default AD ACE equations (Figure 2)

Figure 2. Calibration of Treatment Effect on Amyloid Level During and Beyond Trial Time Horizon



Abbreviations: AD = Alzheimer's disease; CDRSB = Clinical Dementia Rating Scale-Sum of Boxes; MCI = mild cognitive impairment; PET = positron emission tomography; SoC = standard of care; SUVr = standard uptake value ratio

- As a result, a set of calibrated reductions were initially applied to the predicted amyloid PET SUVr values in the model's SoC arm to match the amyloid reduction during the first 18 months of the trial in order to closely match the observed percentage change in CDR-SB over trial duration (i.e., -0.30 mean reduction in amyloid PET SUVr and 26% decline in the rate of change in CDR SB over 18 months)
- Beyond the trial duration, treatment effect was further monitored on the amyloid PET SUVr level to match its mean value across all simulated profiles to approximately 0.9, i.e., the mean amyloid level observed in cognitively normal individuals in the ADNI dataset
- Mortality was modeled in AD ACE by applying hazard ratios (HR) informed from Andersen et al., 2010 to age-specific US general population survival to naturally increase the probability of death across all health states as patients age[11, 12]
- Patient utilities based on disease severity were informed by a systematic literature review and the same utility was used in community and institutionalized settings; caregiver disutilities were considered in the analysis and patients were assumed to have one caregiver[8]

Results

- The rate of disease progression decreased for patients treated with lecanemab + SoC compared with those treated with SoC alone: a 26% slowing of clinical decline on CDR-SB in patients treated with lecanemab corresponded to a 7%, 13%, and 10% reduction in the proportion of patients progressing to mild, moderate, and severe AD dementia, respectively, over a lifetime horizon compared to the standard of care (SoC; Table 2)

Table 2. Base-Case Results

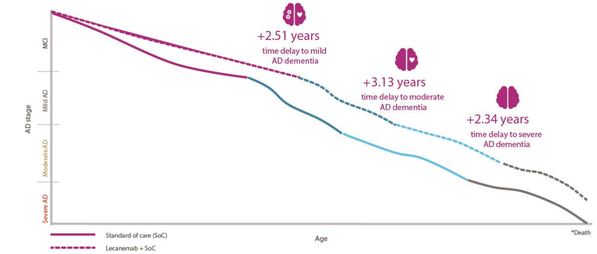
Modeled Health Outcomes	SoC	Lecanemab + SoC	Incremental
Patients with/progressed to mild AD dementia, %	92%	85%	-7%
Patients progressed to moderate AD dementia, %	61%	48%	-13%
Patients progressed to severe AD dementia, %	36%	26%	-10%
Patients institutionalized, %	31%	25%	-6%
Patients discontinued treatment, %	NA	48%	NA
Mean time to event† (undiscounted, years)			
Mild AD	3.10 (2.84–3.42)	5.61 (5.12–6.16)	2.51
Moderate AD	6.14 (5.81–6.54)	9.27 (8.60–10.02)	3.13
Severe AD	9.07 (8.62–9.62)	11.41 (10.74–12.17)	2.34
Institutional care	6.96 (6.56–7.39)	7.70 (7.16–8.28)	0.74
Median time to event (years)			
Mild AD	2.15	3.14	0.99
Moderate AD	5.15	7.10	1.95
Severe AD	8.09	10.10	2.01
Institutional care	6.65	7.34	0.69
Median time to event (of those alive) (years)			
Mild AD	1.84	2.71	0.87
Moderate AD	5.59	9.03	3.44
Severe AD	10.41	NR	NA
Institutional care	15.25	NR	NA
Time on treatment (undiscounted, years)	NA	6.63	NA
Total LYs (undiscounted)	7.37 (7.18–7.55)	8.40 (8.17–8.63)	1.03
Time in community care	6.34	7.50	1.16
MCI due to AD	2.47	3.83	1.36
Mild AD	2.45	2.58	0.14
Moderate AD	1.10	0.89	-0.22
Severe AD	0.33	0.22	-0.11
Time in institutional care	1.02	0.89	-0.13
MCI due to AD	0.00	0.00	0.00
Mild AD	0.14	0.18	0.04
Moderate AD	0.34	0.32	-0.02
Severe AD	0.54	0.38	-0.16
Total LYs (discounted)	6.38	7.11	0.73
Total QALYs (discounted)	4.22 (4.13–4.31)	4.97 (4.85–5.09)	0.75
Patient QALYs, total	4.43	5.15	0.72
Lost to ARIA AEs	NA	0.001	NA
Caregiver QALYs lost	0.21	0.18	-0.03

†The average survival from time 0 to a specified time point was estimated as the area under the survival curve up to that point. Abbreviations: AD = Alzheimer's disease; AE = adverse event; ARIA = amyloid-related imaging abnormalities; LY = life-year; MCI = mild cognitive impairment; NA = not applicable; NR = not reached; QALY = quality-adjusted life-year; SoC = standard of care.

Results (*continued*)

- The mean time to advance to mild, moderate, and severe AD dementia increased by 2.51, 3.13, and 2.34 years, respectively, as compared to SoC (Figure 3)

Figure 3. Delaying clinical decline and disease progression



- The incremental median times to mild and moderate AD (of those alive) were 0.87 and 3.44, respectively, although the median time was not reached for severe AD and institutional care
- Patients treated with lecanemab + SoC were estimated to spend +1.16 more years in community care and -0.13 less years in institutional care compared with the SoC group, which translated into overall incremental survival of 1.03 years (8.40 years for lecanemab + SoC vs. 7.37 years for SoC)
- Compared with SoC, lecanemab treatment improved patient's quality of life over lifetime with additional 0.72 life-years and 0.75 quality-adjusted life-years per patient.
- Scenario analyses indicated the potential lifetime impact of lecanemab was greater at earlier, younger onset AD. The incremental mean times for transition to mild and moderate AD dementia were 3.29 and 3.38 years, respectively, in younger adults (baseline mean age 65 vs. 71.5 years) with MCI due to AD only. (Table 3)

Table 3. Scenario Analysis Results

	QALYs			Mean Time to Mild AD Dementia			Mean Time to Moderate AD Dementia		
Scenarios	**SoC**	**Lecanemab + SoC**	**INC**	**SoC**	**Lecanemab + SoC**	**INC**	**SoC**	**Lecanemab + SoC**	**INC**
Base-case analysis†	4.22 (4.1–4.3)	4.97 (4.9–5.1)	0.75	3.10 (2.8–3.4)	5.61 (5.1–6.2)	2.51	6.14 (5.8–6.5)	9.27 (8.6–10.0)	3.13
MCI due to AD	4.49 (4.4–4.6)	5.31 (5.2–5.4)	0.82	3.07 (2.9–3.4)	5.60 (5.2–6.1)	2.53	6.89 (6.5–7.4)	10.23 (9.6–11.0)	3.34
Mild AD dementia	3.0 (2.9–3.1)	3.36 (3.3–3.4)	0.36	NA	NA	NA	3.30 (3.2–3.5)	4.66 (4.3–5.2)	1.36
Mean baseline age 65	5.07 (5.0–5.2)	6.05 (5.9–6.2)	0.98	3.67 (3.4–4.0)	6.67 (6.2–7.2)	3.00	6.60 (6.3–7.0)	9.60 (9.0–10.2)	3.00
MCI due to AD + mean baseline age 65	5.40 (5.3–5.5)	6.52 (6.4–6.7)	1.12	3.75 (3.5–4.1)	7.04 (6.6–7.6)	3.29	7.42 (7.1–7.8)	10.85 (10.3–11.5)	3.38

†Base-case population: MCI due to AD and mild AD dementia with confirmed Aβ pathology. Abbreviations: Aβ beta-amyloid; AD = Alzheimer's disease; INC = incremental; MCI = mild cognitive impairment; NA = not applicable; QALY = quality-adjusted life-year; SoC= standard of care

Conclusions

- The analysis indicated that treatment with lecanemab could potentially lower the risk of AD dementia or institutional care for patients with MCI. Treatment with lecanemab was also associated with an increase in mean survival compared with SoC.
- The predicted health outcomes provide a foundation for healthcare decision-makers to understand the potential clinical and socioeconomic value of lecanemab.

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