Modelling the Lifetime Effects of Lecanemab in Early Alzheimer's Disease

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INTRODUCTION

- Lecanemab is a humanized monoclonal antibody that has a unique dual mechanism of action, preferentially targeting and clearing the neurotoxic Aβ protofibrils and reducing downstream plaque formation[1, 2]. Consequentially, lecanemab also results in improvements in other biomarkers associated with the underlying pathology of AD, such as biomarkers of tauopathy and of neurodegeneration, which slows down the cognitive and functional decline associated with AD[2, 3].
- Based on the clinical benefit observed in the Phase 3 pivotal study Clarity AD (NCT0388745538), lecanemab has received approval in several countries, including in the European Union (EU) and the United Kingdom (UK), for the treatment of early AD in patients who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes[2, 4-6].

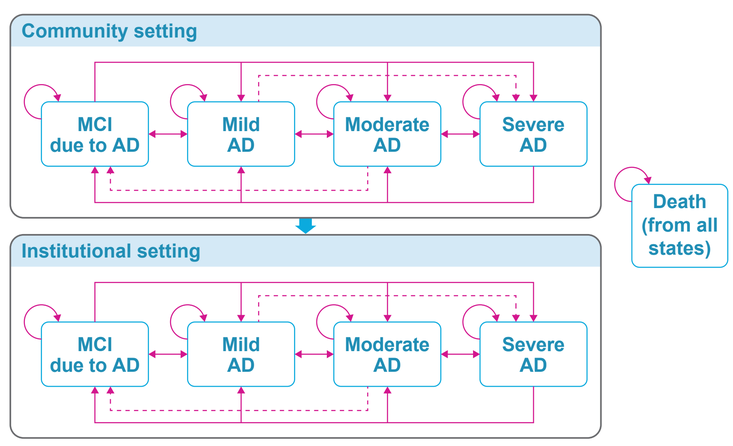
OBJECTIVES

- To assess the long-term effects of lecanemab plus standard of care (SoC) consisting of symptomatic and non-pharmacological treatments compared with SoC alone in a cohort of patients with early Alzheimer's disease (AD; mild cognitive impairment [MCI] due to AD, or mild AD dementia) using different modelling approaches and data from Clarity AD.

METHODS

- A Markov model was employed using health states based on disease severity, long-term institutionalization, and death, with disease severity defined using the Clinical Dementia Rating – Sum of Boxes (CDR-SB) classification for MCI due to AD, and Mild, Moderate, and Severe AD (**Figure 1**).
- State transitions during the first 18 months of treatment were estimated using two alternate approaches
- **In Approach 1**, transition probabilities in Month 0–18 were estimated based on patient count data from the randomized controlled phase of the Clarity AD Core Study (lecanemab + SoC, N=723; SoC, N=743)[2]
- **In Approach 2**, a multistate survival analysis was used to estimate transition probabilities from month 0–18 using a clock-forward (Markov) approach[7], with observations considered using time from baseline to enable time-dependent transition probabilities to be incorporated in the model structure without tunnel states (**Figure 2**).
- Transition probabilities beyond 18 months for the lifetime of the cohort were informed by longitudinal natural history data for the SoC arm with a hazard ratio for time-to-worsening health state applied to estimate outcomes in the lecanemab arm.
- The HR based on CDR-SB for the MCI due to AD subgroup (HR=0.701, 95% CI: 0.564, 0.871) of the Clarity AD Core Study was used for all transitions from the MCI due to AD state and the HR for the Mild AD subgroup (HR=0.584, 95% CI: 0.306, 1.115) was used for all forward transitions from the Mild AD or Moderate AD states.
- A scenario is applied using data from the open label extension of Clarity AD to estimate the HR for lecanemab vs placebo. In the absence of a placebo treatment arm in the 48-month open label extension phase of Clarity AD, a matched observational cohort from ADNI was used as a substitute to predict the natural progression of AD. Cox proportional hazards models were used to calculate the HR for time to worsening for lecanemab vs matched ADNI cohort (combined HR = 0.702, 95% CI: 0.583, 0.845)
- A further scenario is included that estimates the time to worsening HR using a copy increments from control-based multiple imputation approach[8]. This analysis applies an imputation to the missing data in the lecanemab arm assuming those patients revert to the hazard associated with patients in the placebo arm upon discontinuation (MCI due to AD HR = 0.767, 95% CI: 0.626, 0.940; Mild AD HR = 0.516, 95% CI: 0.291, 0.915).

Figure 1. Markov state transition model structure



Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

Figure 2. Multi-state survival analysis structure

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

RESULTS

- Over a lifetime horizon, the model predicted a slower rate of disease progression for lecanemab + SoC compared with SoC. Time to mild AD was delayed by 1.31 years.
- Time to moderate AD and time to severe AD were delayed by 1.85 and 2.04 years, respectively.
- The model also predicted that compared to SoC, lecanemab + SoC increased the time in community care (1.37 years) and reduced time spent in institutional care (-0.02 years).
- Results were similar when using Approach 1 and 2 (**Table 1, Figure 3**).
- Conclusions were similar across scenarios (**Table 2**).

Table 1. Model results

Health state	SoC	lecanemab + SoC	Incremental	SoC	lecanemab + SoC	Incremental
	Approach 1			Approach 2		
Mean time to event, undiscounted, years						
Mild AD	3.07	4.37	1.31	2.89	4.19	1.30
Moderate AD	4.80	6.65	1.85	4.65	6.49	1.84
Severe AD	5.97	8.01	2.04	5.84	7.88	2.04
Mean time in, undiscounted, years						
MCI due to AD	3.07	4.37	1.31	2.89	4.19	1.30
Mild AD	1.73	2.27	0.54	1.76	2.30	0.54
Moderate AD	1.18	1.37	0.19	1.19	1.39	0.20
Severe AD	1.81	1.12	-0.68	1.84	1.15	-0.69
AD	4.71	4.76	0.05	4.79	4.84	0.05
Community care	6.33	7.70	1.37	6.18	7.54	1.36
Institutional care	1.45	1.43	-0.02	1.50	1.48	-0.01
Survival	7.78	9.14	1.36	7.68	9.03	1.35

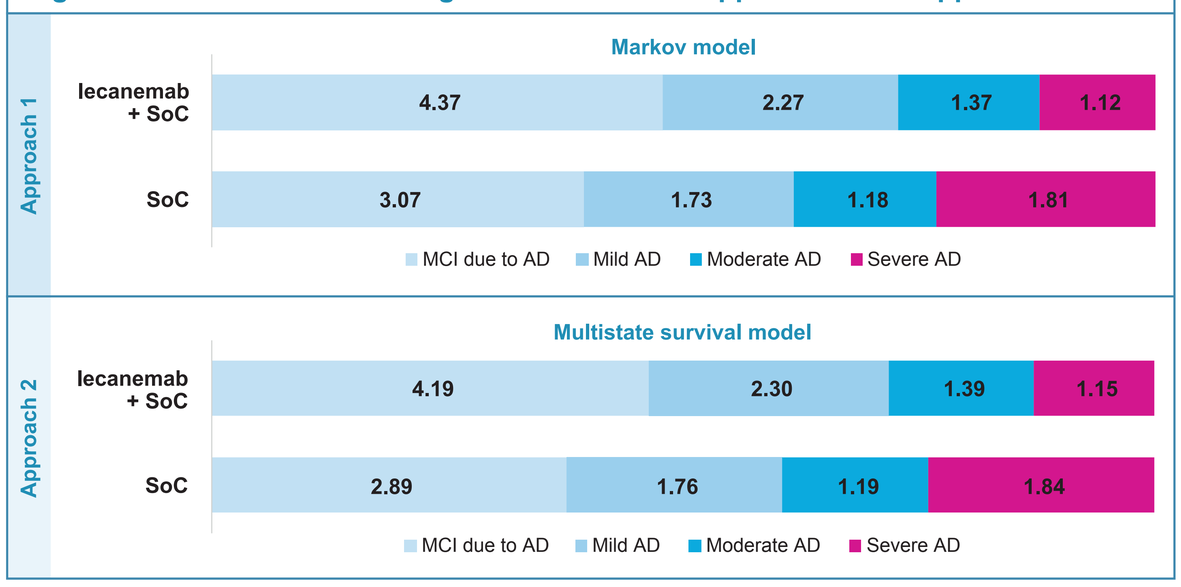
Abbreviations: AD, Alzheimer's dementia; MCI, mild cognitive impairment; SoC, standard of care.

Table 2. Scenario results, mean time to Moderate AD (years)

Scenario	SoC	lecanemab + SoC	Incremental	SoC	lecanemab + SoC	Incremental
	Approach 1			Approach 2		
Base case	4.80	6.65	1.85	4.65	6.49	1.84
TTW HR from OLE (48-months)	4.80	6.23	1.44	4.65	6.08	1.43
TTW HR, copy-increments approach	4.80	6.63	1.83	4.65	6.49	1.83

Abbreviations: AD, Alzheimer's dementia; OLE, open label extension; SoC, standard of care.

Figure 3. Time in state modeling outcomes for the Approach 1 and Approach 2



Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; SoC, standard of care.

CONCLUSION:

- Patients treated with lecanemab + SoC experience delayed progression to Moderate and Severe AD, resulting in additional life years and reduced time in institutional care.
- This information is important for treatment decisions to be made by patients and their families with their clinician's support as well as for payers requiring robust evidence of long-term benefits of lecanemab treatment.

Disclosures for authors and Acknowledgements: This analysis and editorial support was funded by Eisai and Biogen. Please note that the analysis presented in this poster uses the subgroup specific HRs in the base case and differs from the base case analysis in the associated abstract which uses the combined population HR for all health states.

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Poster presented at ISPOR EUROPE 2025 | 9-12 November 2025 | Glasgow, Scotland, UK