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Cost-Effectiveness and Value-Based Pricing of Aducanumab for Patients With Early Alzheimer Disease

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ABSTRACT

Introduction: Aducanumab was granted accelerated approval with a conflicting evidence base, near-unanimous FDA Advisory Committee vote to reject approval, and a widely criticized launch price of $56,000 per year. The objective of this analysis was to estimate its cost-effectiveness.

Methods: We developed a Markov model to compare aducanumab in addition to supportive care to supportive care alone over a lifetime horizon. Results were presented from both the health system and modified societal perspective. The model tracked the severity of disease and the care setting. Incremental cost-effectiveness ratios were calculated, and a threshold analysis was conducted to estimate at what price aducanumab would meet commonly used cost-effectiveness thresholds.

Results: Using estimates of effectiveness based on pooling of data from both pivotal trials, patients treated with aducanumab spent four more months in earlier stages of AD. Over the lifetime time horizon, treating a patient with aducanumab results in 0.154 more QALYs gained per patient and 0.201 evLYGs per patient from the health care system perspective, with additional costs of approximately $204,000 per patient. The incremental outcomes were similar for the modified societal perspective. At the list price of $56,000 per year, the cost-effectiveness ranged from $1.02 million per evLYG to $1.33 million per QALY gained from the health care system perspective; and from $938,000 per evLYG to $1.27 million per QALY gained in the modified societal perspective. The annual price to meet commonly used cost-effectiveness thresholds ranged from $2,950 to $8,360, which represents a discount of 85-95%

off from the annual launch price set by the manufacturer. Using estimates of effectiveness based only on the trial that suggested a benefit, the mean incremental cost was greater than $400,000 per QALY gained.

Discussion: Patients treated with aducanumab received minimal improvements in health outcomes at considerable cost. This resulted in incremental cost-effectiveness ratios that far exceeded commonly used value thresholds, even under optimistic treatment effectiveness assumptions. These findings are subject to the substantial uncertainty regarding whether aducanumab provides any true net health benefit, but evidence available currently suggests that an annual price of aducanumab of $56,000 is not in reasonable alignment with its clinical benefits.

INTRODUCTION

Standard treatment of Alzheimer's Disease (AD) has been focused on supportive care, which historically has included symptomatic medications that do not alter the course of the disease.[1,2] However, on June 7th, 2021, the first potentially disease-modifying treatment for AD, aducanumab (Aduhelm™, Biogen), was granted accelerated approval by the United States' Food and Drug Administration (FDA).[3]

The approval of aducanumab was lauded by some experts as the dawning of a new era in the treatment of AD, but the approval was mired in controversy due to multiple factors: a

complex and conflicting evidence base;[4,5] extensive collaboration between the manufacturer and the FDA in post-hoc data analysis;[6,7] a near-unanimous negative FDA Advisory Committee vote;[8,9] a late switch by the FDA away from standard approval based on cognitive outcomes to an accelerated approval based solely on amyloid clearance;[10,11] and, finally, a widely-criticized launch price of $56,000 per year that would impose steep out-of-pocket burdens on many patients and would also raise the prospect that the drug's cost could exceed spending by Medicare on all other infused drugs combined.[12-14]

At the heart of these concerns lies conflicting evidence from the two pivotal trials of aducanumab. These trials, ENGAGE and EMERGE, were two identically designed, nearly concurrent Phase III randomized controlled trials.[15,16] Following a prespecified interim analysis, both trials were terminated in March of 2019 because an independent data monitoring committee judged they were unlikely to meet their goal of demonstrating benefit through changes in the primary endpoint, the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB).[17] However, following termination of both studies, additional data were received by the manufacturer, and additional analyses found a positive treatment effect on CDR-SB in the EMERGE trial. Results from ENGAGE continued to show no slowing of cognitive decline compared to placebo.[15,16]

In light of the discordant trial results on treatment efficacy, and following a negative vote from the Advisory Committee convened by the FDA to review the data, the FDA changed course and approved aducanumab not on the basis of evidence on cognitive outcomes but on the reduction of beta-amyloid plaques, a surrogate endpoint deemed for the first time by the FDA to be "reasonably likely" to provide patient benefit.[18] However, due to the uncertainty of

improvement in cognitive outcomes and the risk of harms from aducanumab treatment (primarily amyloid-related imaging abnormalities, or ARIA), a decision about treatment presents a dilemma for many patients, families, and clinicians. Given the large size of the population with AD, it is also now poised to become one of the drugs with the highest expenditures in the Medicare system.[12]

The objective of this analysis is to assess the cost-effectiveness of aducanumab by estimating the mean incremental cost per quality-adjusted life year gained at current aducanumab pricing, using various assumptions regarding the clinical benefits of the drug and, importantly, to suggest a treatment price that would reach commonly cited cost-effectiveness thresholds.[19]

METHODS

Study Design

We developed a Markov model to compare aducanumab in addition to supportive care to supportive care alone over a lifetime time horizon. Future costs and outcomes were discounted at 3% per year, with a model cycle length of one year. Results were presented from two perspectives: 1) a health system perspective, including direct medical costs, long-term care, and health outcomes for the patient, and 2) a modified societal perspective, including additional elements such as patient productivity, caregiver quality of life, caregiver time, and caregiver medical costs. Given the average age of the population who have Alzheimer's disease is greater than 65 years of age, the direct medical cost inputs used in our analysis may be most

reflective of a population covered by Medicare. eTable 1 details which elements were included in each perspective.

The Markov model consisted of five health states that tracked the severity of disease, including mild cognitive impairment (MCI) due to AD, mild dementia due to AD, moderate dementia due to AD, severe dementia due to AD, and death (Figure 1). The model schematic is presented in Figure 1. Each arrow represents possible transitions between health states and includes the annual probability for each transition between alive health states, as well as the standardized mortality ratio for each transition to the dead health state. Annual transition probabilities between each of the alive health states represent those consistent with usual care alone and were derived from a recent analysis of AD progression using data from beta-amyloid positive patients in the National Alzheimer's Coordinating Center database.[20] Standardized mortality ratios were applied to age- and sex- adjusted mortality sourced from US-specific tables.

The model also tracked the probability of residing in long-term care, with the probability of transitioning to long-term care varying by health state. Patients were able to transition from community to long-term care; however, once in long-term care, they remained there until death. Individuals remained in the model until they died. Model outcomes included quality-adjusted life years (QALYs) gained, life years (LYs) gained, equal value of life years gained (evLYGs),[21] and total costs. The evLYG is an outcome that evenly measures any gains in life extension, regardless of aducanumab's ability to improve patients' quality of life. Using these model outcomes, we calculated incremental cost-effectiveness ratios to estimate the cost-effectiveness of aducanumab and conducted a threshold analysis on the cost of aducanumab to

estimate at what price it would meet commonly used cost-effectiveness thresholds (e.g., $100,000 per QALY/evLYG and $150,000 per QALY/evLYG).[19]

In alignment with the updated FDA label, the population initiating aducanumab treatment at the start of the model was restricted to those with early AD (defined as MCI due to AD or mild dementia due to AD). Consistent with population estimates, slightly more than half (55%) of the cohort started in the MCI due to AD health state, with the remaining cohort (45%) starting in the mild dementia due to AD health state.[22] Other characteristics of the population starting in the model mirrored the characteristics from the two Phase III trials,[15,16] with an average age of 70 years and 52% female. Given aducanumab involves weight-based dosing, the weight of the population modeled represented the average weight of AD patients from the Aging National Alzheimer's Coordinating Center 2015-2020 data.[23] The majority of the cohort (92%) started the model in a community setting of care.[24] The model was programmed in Microsoft Excel Version 2111.

Model Assumptions

Given the inconsistencies and the uncertainties in the data on the clinical effectiveness of aducanumab, for the base case analysis we pooled results and used a weighted average (based on the sample sizes) of the intention-to-treat results from EMERGE and ENGAGE to estimate the effect of aducanumab on reducing disease progression for health state transitions. Pooling of data from contemporaneous trials is a standard epidemiological approach given both trials had the same research question, similar population and setting, and similar intervention

and implementation approach.[25] To explore results using a different assumption regarding effectiveness, we performed a scenario analysis based on data from the positive EMERGE study only.

Because the vast majority of the patients in both trials had MCI due to AD (rather than mild dementia due to AD) at baseline, the only direct transition evidence was on the rate of transition from the MCI due to AD heath state to the mild dementia due to AD health state. Therefore, likely effects of treatment on relative rates of transition from mild dementia due to AD to moderate dementia due to AD and further to severe dementia due to AD were informed by clinical experts. In the base case analysis, the impact of aducanumab on the transition from mild dementia due to AD to moderate dementia due to AD was assumed to be half of its effectiveness in slowing transition from MCI due to AD to mild dementia due to AD. Clinical experts also suggested that once a patient has reached moderate dementia due to AD, there is likely no additional treatment effect from moderate dementia due to AD to severe dementia due to AD; therefore, we modeled no treatment effectiveness after a patient reached moderate dementia due to AD. We also did not model any possibility for a worsening or "catch-up" of treated patients that would lead to a transitioning to severe dementia due to AD at a faster rate than would be experienced by patients on supportive care alone. These treatment effectiveness assumptions were extensively tested through sensitivity analyses.

We also used evidence from both Phase III trials to inform assumptions around treatment discontinuation over the trial time horizon. No discontinuation due to adverse events was assumed after the trial time horizon due to consistent findings that ARIA occurs at the beginning of the treatment course.[26] In addition to discontinuation due to adverse events

occurring within the first 18 months of treatment initiation, we assumed patients discontinued aducanumab treatment once they reached severe dementia due to AD. These discontinuation assumptions were also extensively tested through sensitivity analyses.

Model Inputs

The primary clinical inputs included the transition probabilities among alive health states, mortality, progressions to long-term care, treatment effectiveness, the occurrence of ARIA, and treatment discontinuation. The transition probabilities without treatment were from a recent analysis of AD progression using data from beta-amyloid positive patients from the National Alzheimer's Coordinating Center database.[20] The relative risk of death based on severity of dementia[22] was applied to age- and sex-adjusted all-cause mortality. Progressions to long-term care were estimated separately for each disease stage and were identified from a literature source that calculated these progressions using the Consortium to Establish a Registry for Alzheimer's Disease data.[27] Treatment effectiveness was measured using CDR-SB data reported in the pivotal trials and manufacturer provided hazard ratios on observed transitions, where available.[26] Data on the occurrence of ARIA and treatment discontinuation were sourced directly from the two pivotal trials.[26] Health state utilities for both the patient and caregiver were derived from publicly available literature. These utility estimates primarily came from a cross-sectional study of AD patients and caregivers with stratifications for both disease severity and setting of care.[27-29]

The primary cost inputs included aducanumab acquisition costs, administration costs, monitoring costs, adverse event costs, long-term care costs, and other patient medical and pharmacy costs. Costs resulting from the diagnostic imaging (e.g., amyloid positron emission tomography scan, lumbar puncture) or genetic testing (e.g., for apolipoprotein E ε4) that may be done for diagnosis prior to initiating aducanumab were not included given these are upstream from treatment initiation and would also occur in patients who do not subsequently receive aducanumab. Treatment acquisition costs were sourced from Redbook, and an additional 6% was added to the cost of aducanumab to account for the clinician add-on reimbursement fee by the Centers for Medicare and Medicaid Services. Administration, monitoring, and adverse event costs were sourced from the Centers for Medicare and Medicaid Services Physician Fee Schedule.[30] Costs of long-term care were identified from a recent report from the Administration on Aging[31] on average cost of a skilled nursing facility in the United States. Patient medical costs were identified from a population-based study of AD patients aged 70 to 90 years of age.[32] From this study, an AD health state specific multiplier was calculated and applied to age-adjusted health care costs for the US general population, most of which are covered by Medicare given the age of the population. To capture other pharmacy costs not related to aducanumab, we assumed 33.3% of mild dementia due to AD patients received generic donepezil and 33.3% of moderate dementia due to AD patients received generic memantine.[33] Price estimates for these generic drugs were sourced from Redbook.[34,35]

Costs to inform the modified societal perspective also included patient and caregiver productivity, and caregiver health care costs. A study published in 2020 reported estimates on patient productivity losses and caregiver time spent.[36] Estimates from this study were

multiplied by an average hourly wage to monetize this lost productivity.[37] This 2020 study also reported caregiver direct medical costs for caregivers[36] which were used in the model. Primary model inputs are presented in Table 1, with a full list of model inputs to promote transparency and validation available elsewhere.[5]

Scenario and Sensitivity Analyses

We conducted numerous scenario analyses given the uncertainty in some of the model assumptions, primarily aducanumab treatment effectiveness and discontinuation. We present a scenario analysis that makes more favorable assumptions than our base-case analysis, as well as a scenario analysis that makes less favorable assumptions than our base-case analysis. In our optimistic scenario analysis, we first assumed the effectiveness of aducanumab was based on the findings from the EMERGE trial only. In a stepwise approach, we then added two other optimistic assumptions: 1) the effectiveness of aducanumab in reducing progression of mild dementia due to AD to moderate dementia due to AD is equally as effective as it is on MCI due to AD to mild dementia due to AD; and 2) aducanumab treatment is discontinued once a patient enters moderate dementia due to AD instead of severe dementia due to AD, with no "catch-up" decline in cognition. In our conservative scenario analysis, we first assumed that aducanumab was not effective on transitions out of mild dementia due to AD (but assumed the blended hazard ratio from both trials on the transition out of MCI). As an added layer on the conservative scenario analysis, we then assumed the hazard ratio on the transition out of MCI due to AD was based on findings from the ENGAGE trial only.

Further, we conducted one-way sensitivity analyses to identify the key drivers of cost-effectiveness. We varied the input parameters using available measures of parameter uncertainty (i.e., standard errors where available or reasonable ranges) to evaluate changes in the incremental cost-effectiveness ratios when a single input was varied. Further, probabilistic sensitivity analyses were conducted to vary all inputs with noted uncertainty simultaneously. In these sensitivity analyses, the inputs were varied across plausible ranges, informed by reported standard errors and confidence intervals where available. In the absence of a reported standard error or confidence interval, we assumed the standard error was 10% of the deterministic value. In the probabilistic sensitivity analysis, a value was drawn from a distribution. Hazard ratios and relative risks followed a gamma distribution; probabilities followed a beta distribution; and utility inputs followed a normal distribution.

Standard Protocol Approvals, Registrations, and Patient Consents

This work did not constitute human subject research and thus no institutional review board approval or consent was needed.

RESULTS

Base-Case Results

Using estimates of effectiveness based on pooling of data from both pivotal trials, a patient treated with aducanumab spent more time in earlier stages of AD than a patient treated with supportive care alone, equating to approximately three more months in MCI due to AD and one more month in mild dementia due to AD. Over the lifetime time horizon, treating a patient with aducanumab resulted in 0.154 more QALYs gained per person and 0.201 evLYGs per person, with additional costs of approximately $204,000 per person treated. QALY gains were essentially split between improvements in utility (47% of gains) and extension in survival (53% of gains). Because the clinical improvements were so small, the cost-effectiveness results were very similar when performed with the impact on patient productivity and on caregivers added as part of a modified societal perspective. The model outcomes are presented in Table 2.

The incremental cost-effectiveness ratios for the incremental cost per QALY gained, incremental cost per evLY gained, and incremental cost per life year gained are presented in Table 3. At the list price of $56,000 per year, the cost-effectiveness ranged from $1.02 million per evLYG to $1.33 million per QALY gained from the health care system perspective. From the societal perspective, the cost-effectiveness ranged from $938,000 per evLYG to $1.27 million per QALY gained.

Table 4 presents the results from the threshold analyses that calculate the annual cost at which aducanumab would meet commonly cited value thresholds from $100,000 to $150,000 per evLYG or QALY gained. The annual price to meet these thresholds ranged from $2,950 to $8,360, which represents a discount of 85-95% off from the annual price set by the manufacturer.

Scenario Analyses

Table 5 presents the results from the optimistic and conservative scenario analyses. Incremental cost-effectiveness ratios under various optimistic assumptions ranged from $334,000 to $598,000 per QALY gained. Under these optimistic scenarios, an annual fair price could range from $9,000 to $26,000. The most favorable incremental cost-effectiveness ratio was approximately $350,000 per QALY gained, and that was making numerous optimistic assumptions including that the aducanumab effectiveness was based on evidence from the EMERGE trial only, that aducanumab was equally as effective on mild dementia due to AD progression as it was on MCI, and patients would discontinue aducanumab treatment once they reached moderate dementia due to AD without "catch up" worsening of dementia. Incremental cost-effectiveness ratios under various conservative assumptions ranged from $1.27 million per QALY gained to being dominated (i.e., more costly, less effective) by supportive care. The least favorable cost-effectiveness estimate suggested that aducanumab was dominated (e.g., more costly, less effective) by supportive care, which occurred when we assumed aducanumab was not effective at delaying progression as suggested by the ENGAGE trial.

Sensitivity Analyses

The effectiveness of aducanumab on delaying progression of AD predominated the one-way sensitivity analysis and had the largest impact on the cost-effectiveness of aducanumab. Incremental cost-effectiveness ratios for aducanumab compared to supportive care ranged from dominated (i.e., more costly, less effective) when the hazard ratio on delaying progression of MCI due to AD to mild dementia due to AD were greater than 1.0, in alignment with what was observed in the ENGAGE trial, to estimates of around $600,000 per QALY gained when the hazard ratio on delaying progression to mild dementia due to AD were more closely aligned with what was observed in the EMERGE trial. The probability of symptomatic ARIA influenced the cost-effectiveness findings, but in a much smaller magnitude as compared to the assumptions around treatment effectiveness. The probabilistic sensitivity analysis did not produce any cost-effectiveness estimate beneath commonly cited value thresholds from either the health care system or the societal perspective. The one-way sensitivity analysis produced negative incremental cost-effectiveness ratios (resulting from a negative incremental QALY gained) for some inputs, thus we plot the incremental QALYs and incremental costs separately. Figure 2 provides the results of the one-way sensitivity analysis for incremental QALYs. eFigure 1 provides the results for incremental costs. The results from the probabilistic sensitivity analysis are presented on the cost-effectiveness plane in eFigure 2.

DISCUSSION

Our base-case analysis suggests that over a lifetime time horizon, patients treated with aducanumab received minimal improvements in health outcomes at considerable cost. This resulted in incremental cost-effectiveness ratios that far exceeded commonly cited value thresholds, even under the most optimistic treatment assumptions. Under our base-case assumptions of effectiveness of aducanumab based on pooled trial data from EMERGE and ENGAGE, the threshold analyses calculated that aducanumab would need to be priced between $2,950 and $8,360, a discount of 85%-95% from the list price, for an annual course of treatment to meet commonly cited value thresholds. In the optimistic scenarios, which only considers data from the favorable EMERGE trial alongside other optimistic assumptions, the threshold analyses would suggest higher aducanumab prices ($9,000 to $26,000 per year) than those using our base-case assumptions; however, discounts of 55%-84% would still be needed from the price set by the manufacturer to meet commonly cited value threshold. In the conservative scenario that only included the negative trial ENGAGE, the threshold analysis would not suggest any price for aducanumab that could be aligned with value.

The cost-effectiveness of aducanumab in the modified societal perspective was very similar to the health care system perspective, despite the known large impact of AD on caregivers.[38-42] As noted earlier, the results were comparable across perspectives due to the small impact of aducanumab on disease progression. A more effective treatment for AD would

have substantial "spillover" effects for caregivers and for society that would have a major impact on cost-effectiveness and suggested value-based pricing from the societal perspective.

Our analysis is limited primarily by the uncertainty resulting from the inconsistency in evidence on the effectiveness of aducanumab. In addition, neither EMERGE nor ENGAGE produced evidence to guide assumptions about the impact of treatment on transitions from mild dementia due to AD to moderate dementia due to AD and on to severe dementia due to AD. Based on the theory of the impact of amyloid clearance on downstream clinical effects it seems most likely to clinical experts that aducanumab would not have comparable benefits at slowing transitions at those later stages, but this remains an important gap in the currently available evidence. Finally, estimates on utilities for patients and caregivers were obtained from cross-sectional studies that might be limited in their ability to capture changes over time and may not be sensitive enough to detect AD-specific consequences. To account for this in the analyses, these utility values were varied over a wide range in the sensitivity analyses, but additional research among preference and utility elicitation among AD patients and caregivers is needed.

Cost-effectiveness analysis can serve as an evidence-based foundation of considerations regarding long-term value at different pricing levels of new treatments, but other factors should be integrated into policy decisions.[19] Relative certainty about the data, potential benefits beyond those measurable in clinical trials, the relative contribution of federal sponsors to the costs of research and development, social and ethical considerations, and the potential size of the treated population are all important factors in broader judgments of value and fair pricing. In the case of aducanumab, the potential "financial toxicity" to patients and families

cannot be ignored given the 20% co-insurance requirement for out-of-pocket payments for infused agents in Medicare.[12] The potential harm to Medicare budgets and resulting premiums for all Medicare beneficiaries is also one of these factors that should be integrated into considerations about reasonable pricing.

Nonetheless, cost-effectiveness analysis can provide a tangible starting point for these considerations, and scaling the price for new interventions in proportion to their estimated benefits to patients and impact on other costs in the health care system and society is often viewed as a helpful way to incentivize innovation that can benefit patients without creating more harm than good. The results of our analyses suggest, unfortunately, that aducanumab does not have the evidence to support a robust clinical effect, and that its price would need to be dramatically reduced to represent a reasonable value for its uncertain benefits.

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Table 1: Model Inputs

Aducanumab Effectiveness		
Health States	**Hazard Ratio**	**Source/Notes**
MCI Due to AD	X.XX*	Calculated based on the weighted average from each trial; used 1.02 for ENGAGE trial[26] based on CDR-SB and X.XX* for EMERGE trial based on health state transition evidence from the manufacturer
Mild Dementia due to AD	50% as effective as hazard ratio for the MCI due to AD health state	Clinical experts' opinion; applied to the mild dementia due to AD to moderate dementia due to AD and mild dementia due to AD to severe dementia due to AD transitions
Moderate Dementia due to AD	1.0	Clinical experts' opinion
Progression to Long-Term Care		
Health States	**Value**	**Source/Notes**
MCI Due to AD	2.4%	Calculated based on the reported mild dementia due to AD annual transition probability and relationship between relative risk of death for MCI due to AD and mild dementia due to AD
Mild Dementia Due to AD	3.8%	Neumann et al., 1999[27]
Moderate Dementia Due to AD	11.0%	
Severe Dementia Due to AD	25.9%	
Adverse Events from Aducanumab Treatment		
Parameter	**Value**	**Source/Notes**
Probability of ARIA-E	30.7%	FDA Advisory Committee Briefing Document[16]
Probability of ARIA-H	25.1%	
Concurrent ARIA-E and ARIA-H	17.9%	
Probability of Symptomatic ARIA	10%	
Probability of Discontinuation due to Adverse events	10%	
Disutility of ARIA	-0.14	Disutility estimate for headache, which was the most reported symptom of ARIA;[43] Applied for a duration of 12 weeks to patients experiencing symptomatic ARIA[16]
Cost of ARIA	$765.99	Equivalent to the price of three

		brain MRIs[30]
Patient Disutility (Community; LTC)		
Health State	**Disutility**	**Source/Notes**
MCI Due to AD	-0.17; -0.17	Calculated from utility estimates and patient demographics in Neumann et al., 1999[27,28]
Mild Dementia due to AD	-0.22; -0.19	
Moderate Dementia due to AD	-0.36; -0.42	
Severe Dementia due to AD	-0.53; -0.59	
Caregiver Disutility (Community; LTC)†		
Health State	**Disutility**	**Source/Notes**
MCI Due to AD	-0.03; -0.03	Calculated from utility estimates and patient demographics in Neumann et al., 1999[27,28]; adjusted for AD severity using relationship from Mesterton et al., 2010[29]
Mild Dementia due to AD	-0.05; -0.05	
Moderate Dementia due to AD	-0.08; -0.08	
Severe Dementia due to AD	-0.10; -0.10	
Cost Inputs Annual Cost‡		
Parameter	**Value**	**Source/Notes**
Aducanumab Annual Cost	$56,000	Manufacturer[44]; Plus 6% due to infusion; first-year cost was $41,344 due to dose titration in first year
IV Administration Cost	$74.58 per administration	HCPCS Code 96365[30]
Brain MRI Cost	$255.33 per scan	HCPCS Code 70553[30]; three brain MRIs in the first year of treatment; three brain MRIs for each occurrence of ARIA
Caregiver Time Spent Caregiving for Community-Dwelling Patients		
Health State	**Time/month**	**Source/Notes**
MCI Due to AD	69 hours/month	Robinson et al., 2020[36] and Haro et al., 2014[45]; Estimates are for amyloid-positive patients where available; caregiver time spent caregiving for LTC-dwelling patients was 44% of time spent for community-dwelling patients[46]
Mild Dementia due to AD	113 hours/month	
Moderate Dementia due to AD	169 hours/month	
Severe Dementia due to AD	298 hours/month	

AD=Alzheimer's Disease; ARIA=amyloid-related imaging abnormality; ARIA-E=amyloid-related imaging abnormality edema type; ARIA-H=amyloid-related imaging abnormality hemorrhagic type; IV=intravenous; LTC=long-term care; MCI=mild cognitive impairment due to AD; MRI=magnetic resonance imaging

*Values were provided from the manufacturer and are academic in confidence at this time.

Table 2. Model Outcomes Per Patient Comparing Aducanumab to Supportive Care from the Health Care System and Modified Societal Perspective Perspectives

	Health Care System Perspective					
Treatment	**Drug Costs**	**Other Costs**	**Total Costs**	**QALYs**	**evLYs**	**Life Years**
Aducanumab	$199,000	$347,000	$546,000	3.467	3.513	5.969
Supportive Care	$0	$342,000	$342,000	3.313	3.313	5.827
Incremental	$199,000	$5,000	$204,000	0.154	0.201	0.143
	Modified Societal Perspective					
Treatment	**Drug Costs**	**Other Costs**	**Total Costs**	**QALYs**	**evLYs**	**Life Years**
Aducanumab	$199,000	$639,000	$838,000	3.097	3.154	5.969
Supportive Care	$0	$636,000	$636,000	2.938	2.938	5.827
Incremental	$199,000	$3,000	$202,000	0.159	0.215	0.143

evLYG=equal value of life year gained; QALY=quality-adjusted life year

Table 3. Incremental Cost-Effectiveness Ratios from the Health Care System and Modified Societal Perspective Perspectives

Perspective	**Comparison**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**
Health Care System	Aducanumab vs. Supportive care	$1,330,000	$1,020,000	$1,430,000
Perspective	**Comparison**	**Cost per QALY Gained**	**Cost per evLYG**	**Cost per Life Year Gained**
Modified Societal	Aducanumab vs. Supportive care	$1,270,000	$938,000	$1,420,000

evLYG=equal value of life year gained; QALY=quality-adjusted life year

Table 4. Results from the Threshold Analysis on the Annual Aducanumab Cost*

Health Care System Perspective	Annual Price Set by Manufacturer	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount Needed to Reach Threshold
QALYs Gained	$56,000	$2,950	$5,110	91%-95%
evLYG	$56,000	$4,260	$7,090	87%-92%
Modified Societal Perspective	**Annual Price Set by Manufacturer**	**Annual Price at $100,000 Threshold**	**Annual Price at $150,000 Threshold**	**Discount to Reach Threshold Prices**
QALYs Gained	$56,000	$3,740	$5,960	89%-93%
evLYG	$56,000	$5,330	$8,360	85%-90%

evLYG=equal-value of life years gained; QALYs=quality-adjusted life years,

*Costs associated with a mark-up or add-on reimbursement fee (e.g., 6% clinician add-on reimbursement fee by the Centers for Medicare and Medicaid Services) would be in addition to these prices. Therefore, the prices in this table meet the threshold even when an additional 6% are added to them.

Table 5. Results from the Scenario Analyses

Optimistic Scenario Analyses	**Cost-Effectiveness from the Health Care System Perspective**	**Cost-Effectiveness from the Societal Perspective**
Base-Case	$1.33 million per QALY gained	$1.27 million per QALY gained
+ Aducanumab effectiveness on MCI due to AD progression was from EMERGE only	$598,000 per QALY gained	$566,000 per QALY gained
+ Aducanumab effectiveness on MCI due to AD progression was from EMERGE only + Aducanumab effectiveness on Mild Dementia due to AD progression was equally as effective as it was for MCI due to AD	$454,000 per QALY gained	$431,000 per QALY gained
+ Aducanumab effectiveness on MCI due to AD progression was from EMERGE only + Aducanumab effectiveness on Mild Dementia due to AD progression was equally as effective as it was for MCI due to AD + Treatment discontinuation upon entry into Moderate Dementia due to AD	$354,000 per QALY gained	$334,000 per QALY gained
Conservative Scenario Analyses	**Cost-Effectiveness from the Health Care System Perspective**	**Cost-Effectiveness from the Societal Perspective**
Base-Case	$1.33 million per QALY gained	$1.27 million per QALY gained
+ Aducanumab does not have an effect on delaying progression once a patient has reached Mild Dementia due to AD	$1.96 million per QALY gained	$1.86 million per QALY gained
+ Aducanumab does not have an effect on delaying progression once a patient has reached Mild Dementia due to AD + Aducanumab effectiveness on MCI due to AD progression was from ENGAGE only	More costly, less effective	More costly, less effective

AD=Alzheimer's disease; MCI=mild cognitive impairment; QALY=quality-adjusted life year

Figure Legend

Figure 1: Model Structure

The arrows between the alive health states reflect the transition probabilities representative of supportive care alone. Evidence suggested low probabilities of patients going to less severe dementia due to AD even among standard of care, although this was uncommon and likely driven by subjective measures of disease classification. In the arm of the model that included patients treated with aducanumab, hazard ratios were applied to these transition probabilities. The numbers on the arrows to the dead health state represent risk ratios (RRs) that were multiplied by age- and sex-adjusted all-cause mortality[20,22]

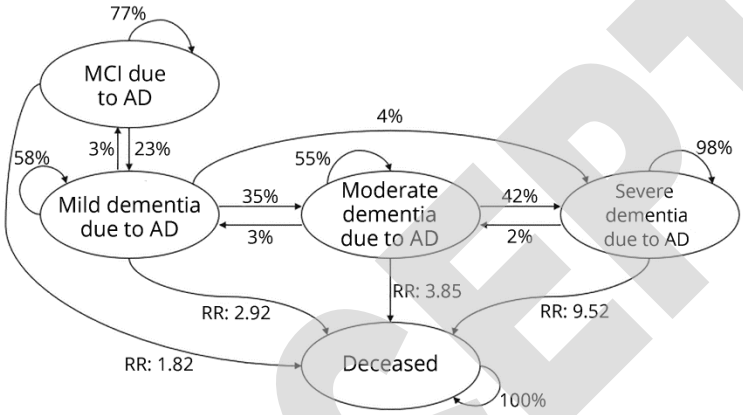
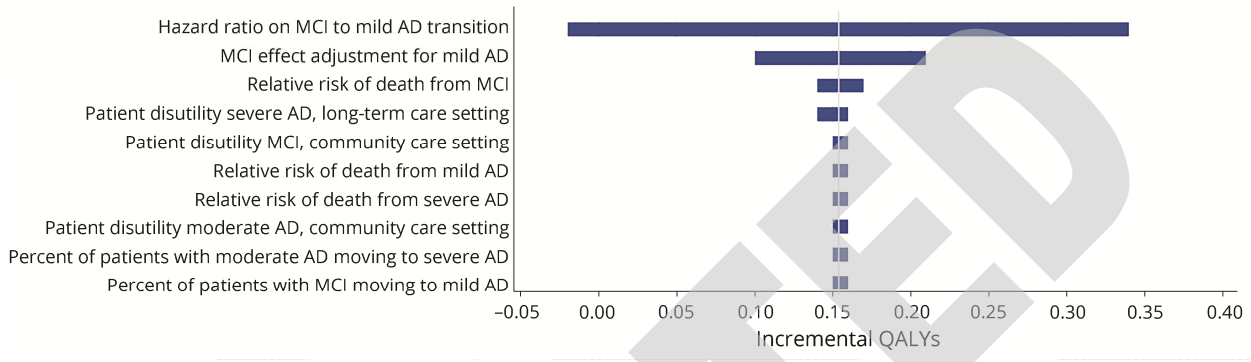


Figure 2. Results from the One-Way Sensitivity Analysis, Incremental QALYs

AD: Alzheimer's disease, MCI: mild cognitive impairment, QALY: quality-adjusted life year



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