

Cost-Effectiveness of Delaying Alzheimer's Disease Progression with Novel Monoclonal
Antibodies

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Abstract

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Background: In the US alone, most of over 7.2 million older adults with Alzheimer's Disease (AD) treat their AD with symptom-relieving therapies. Starting in 2021, three disease-modifying monoclonal antibodies (mAbs) entered the US market as the first disease-modifying treatments for early Alzheimer's disease (AD). Despite years of presence in the US market, the value of these mAbs remains uncertain due to high treatment-related costs and an unclear comparative value of their clinical benefit.

Objectives: 1) To estimate the cost-effectiveness of adding aducanumab, lecanemab, or donanemab to the current standard of care (SOC) and 2) to evaluate the value of reducing uncertainties around the mAbs from a US health care perspective and a modified societal perspective.

Methods: A Markov simulation model was developed by incorporating literature and a prior cost-impact model of delaying AD progression. The clinical benefit and cohort's characteristics mirrored results from phase 3 clinical trials of the three agents. The price of the agents was estimated using wholesale acquisition costs published by Micromedex® RED BOOK®. The

model used a 1-week cycle length and estimated 10-year cost impact and comparative incremental cost-effectiveness ratios (ICERs) among the SOC and the mAbs. Results were described from both a health care sector and a societal perspective. One-way sensitivity analysis was conducted to demonstrate key drivers of cost-effectiveness of the mAbs. Cost-effectiveness acceptability curve and the expected value of perfect information (EVPI) used probabilistic sensitivity analysis to demonstrate the comparative value of the mAbs and the value of resolving uncertainties.

Results: The three agents were estimated to delay progression from MCI to severe AD by 6.2 - 9.2 months. The analysis showed that SOC costs \$243,300 and \$757,800 from the health care sector and the modified societal perspective, respectively, over 10 years. From the health care sector perspective, the mAbs incurred additional \$55K, \$73K, and \$82K for aducanumab, lecanemab, and donanemab, respectively. From the modified societal perspectives, donanemab added \$73K, and aducanumab and lecanemab added \$48K and \$64K to the cumulative costs, respectively. Donanemab had the higher comparative ICER at \$304,200/QALY, followed by lecanemab at \$175,300/QALY. Key driving factors of ICER among lecanemab and donanemab were age at the treatment initiation, patient health state utility values in earlier AD states, and the drug acquisition costs across both perspectives. SOC had more favorable cost-effectiveness at a WTP of \$150K/QALY across both perspectives, and lecanemab was more favored at a WTP of \$200K/QALY. The EVPI of the decisions around lecanemab versus SOC was estimated to be \$143 million at WTP of \$190K/QALY and \$155K/QALY for the health care sector and the modified societal perspectives, respectively. The EVPI around donanemab versus lecanemab was approximately \$109 million at the WTP of \$300K/QALY and \$275K/QALY for the healthcare sector and the societal perspectives, respectively.

Conclusion: In the model simulation, the novel AD treatments incurred substantial costs with modest clinical benefits, with donanemab adding the highest cost. Assuming the treatment costs based on WAC, only lecanemab was found likely to be cost-effective under a WTP of \$200K/QALY from the modified societal perspective. The cost-effectiveness of the mAbs is substantially influenced by the patient's age at the treatment initiation, patient health state utility values at earlier AD states, and the drug acquisition costs.

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1. INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder of unclear pathogenesis and the leading cause of dementia, affecting 6.9 million people aged over 65 years in the United States alone. (1,2) The national economic burden of AD or other dementias among the older population continues to rise, with an estimated cost of \$360 billion in 2024.¹ The disease not only imposes a profound burden on patients and their families but also places considerable pressure on healthcare systems and societal resources due to its progressive course and the absence of a definitive treatment that dramatically slows or reverses the disease.

Patients with AD progress through four distinct stages: mild cognitive impairment (MCI), mild AD, moderate AD, and severe AD.⁴ Each stage is associated with increasing levels of cognitive and functional disability, requiring higher levels of care and support. The progression eventually leads to death, with a substantial impact on patients' quality of life and economic outcomes.² Mortality risk is significantly higher in patients with advanced AD stages, as patients' overall health is exacerbated by comorbidities.^{5,6}

Before 2021, the management strategies for AD were largely limited to symptom management targeting alleviation of moderate-to-severe cognitive and functional decline.² In 2021, a novel therapy, Aduhelm (Aducanumab), was approved by the FDA after displaying a meaningful effect on delaying AD progression in early AD patients.⁷ FDA approval of drugs in the same class, Leqembi (Lecanemab) and Kinsula (Donanemab), soon followed. These drugs demonstrated even greater efficacy in slowing disease progression in early AD patients.^{8,9}

Aduhelm, Leqembi, and Kinsula are anti-amyloid monoclonal antibodies (mAbs) that target formation of amyloid-beta, a key hallmark of AD pathology, and slow progression of disease. Phase 3 clinical trials for these therapies showed a reduction in disease progression ranging from approximately 22-29% compared to placebo.¹⁰⁻¹² Despite these advancements, adoption of these therapies remains limited due to their high costs. Wholesale acquisition costs (WAC) in 2025 range between \$2,100 and \$2,800 per month, excluding costs associated with administration or the management of adverse effects.¹³⁻¹⁵ These treatments require intravenous infusions administered in healthcare clinics, potentially imposing further financial burdens on patients, care partners, and healthcare systems.¹⁶⁻¹⁸ As a result, the cost-effectiveness of these therapies remains unclear.

Given the rapidly growing aging population and the emergence of novel treatments, there has been an increasing need to understand the economic implications of AD. This study aims to develop a simulation model of AD progression in patients with MCI to 1) estimate the cost-effectiveness of adding the novel mAbs to the AD standard of care (SOC) from a US health care sector perspective and a modified societal perspective, and 2) evaluate the uncertainty and value of additional research for each of the three treatment strategies when compared to SOC. Scenario analyses were conducted to assess an enhanced therapeutic benefit assumption and varying discounted drug pricing strategies from the US health care sector and the modified societal perspectives.

2. METHODS

This study follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.¹⁹

2.1. Model Overview

This study adapted a previously developed simulation model of AD progression.²⁰ Building on the framework, the model was structured to perform economic evaluation of the novel mAbs, aducanumab, lecanemab, and donanemab. The model used data on disease progression, costs of care, productivity, health state utility values, rates of institutionalization, mortality, and other mAbs-relevant factors. Parameters were sourced from the peer-reviewed and gray literature, including reports from the Institute for Clinical and Economic Review (ICER) and US Bureau of Labor Statistics. The model employed a 1-week cycle and 10-year time horizon to capture the precise impact of mAbs on cost and health effects amid the rapid progression of AD.

2.2. Perspectives

The cost-effectiveness analysis using the simulation model was conducted from a US health care sector perspective and a modified societal perspective. The US health care sector perspective included patient utility and healthcare and out-of-pocket costs, and the modified

societal perspective additionally included care partner disutility and costs from patient's non-healthcare, patient productivity, care partner productivity, and care partner healthcare.

2.3. Simulation Cohort

The characteristics of the simulation cohort were designed to mirror the baseline characteristics of the early AD patients across the phase 3 clinical trials of Aducanumab (NCT02484547; NCT02477800), Lecanemab (NCT03887455), and Donanemab (NCT04437511).¹⁰⁻¹² The mean age, proportion of male participants, and baseline Clinical Dementia Rating – Sum of Boxes (CDR-SB) score were calculated by taking a weighted average of the reported demographics from the three trials.

2.4. CDR-SB Trajectory Curve of AD progression

The model used a multivariate continuous-time disease progression (MCDP) function developed by Kühnel and colleagues to estimate a progression trajectory in early AD patients by their change in CDR-SB score.²² The model was based on data of 2,152 individuals with more than 10 years of follow-up times in the Alzheimer's Disease Research Initiative (ADNI) database.²² Cohorts in the ADNI database were previously reported to take medication for AD including donepezil, galantamine, rivastigmine, memantine, benzodiazepines, and antidepressants, all of which are still common AD treatments at the time of this research.^{2,23} Given that the first novel mAbs for AD, aducanumab, was approved and commercialized in 2021, we assumed that the ADNI sample population used the conventional AD medication regimen which we defined in our model as SOC.

Our model referenced Kühnel's MCDP model to estimate the progression in early AD patients who received the SOC, and to extrapolate progression in patients received the three mAbs by synthesizing the treatment efficacy estimates into the MCDP equation [See *Methods 2.5.4 Treatment Benefits*]. The projected CDR-SB outcomes were converted into AD stages according to the established conversion scale.⁴ [See *Methods 2.4. Health States*] The equation and the visual presentation of the MCDP model are presented in *Figure 1*.

2.5. Health States

There were five health states in this model, which were four AD states and death. The four AD states – MCI, Mild AD, Moderate AD, and Severe AD – were mapped by CDR-SB score using an established conversion scale⁴ as presented in [Table 1](#).

2.6. Model Inputs

Given limited post-marketing data on mAbs, model parameters were selected based on available literature to capture key outcomes essential for evaluating the impacts of mAbs across all AD states. A summary of these parameters is provided in [Table 2](#).

2.6.1. Treatment Benefit

The treatment efficacy of the mAbs were sourced from Phase 3 clinical trials¹⁰⁻¹² and established network meta-analyses.²⁴ For the base case analysis, we used the trials data to obtain the mean change in CDR-SB scores for between the treatment and placebo groups at the end of each study period, converted into a weekly rate estimate of CDR-SB change, and synthesized to the MCDP-model-based trajectory to extrapolate AD progression in each treatment arm during the time horizon. Each clinical trial included multiple treatment arms with varying dosing regimens. The trials referenced for this research included multiple treatment arms that received various dosing regimen. For this analysis, we only considered the clinical results from the trial arm that received the FDA recommended maintenance doses, as specified in the mAbs package inserts (Aducanumab: 10mg/kg IV every 4 weeks; Lecanemab: 10mg/kg IV every 2 weeks; Donanemab: 1400mg IV every 4 weeks).¹⁶⁻¹⁸ In the US, the mAbs are only indicated for MCI and Mild AD due to AD due to the lack of evidence showing mAbs slowing disease progression in Moderate AD and Severe AD.¹⁶⁻¹⁸ Thus, we assumed the treatment efficacy stops once patients reach Moderate AD. [See [Table 2](#)] Treatment efficacy estimates from a network meta-analysis were incorporated in a scenario analysis. [See *Supplemental Appendix - Scenario Analysis 1*]

2.6.2. Monitoring

The latest professional guidelines on the mAbs recommend clinicians to follow a drug-specific magnetic resonance imaging (MRI) schedule to assess patient eligibility for mAbs and surveil for any amyloid-related imaging abnormalities (ARIA) during the initial doses of therapy.²⁵⁻²⁷ The recommended MRI schedule for each mAb was applied to the corresponding treatment arm and linked to the cost outcomes associated with the monitoring requirement.

2.6.3. Adverse Events

The analysis considered four mAbs-related adverse events (AEs): mild-moderate symptomatic ARIA, headache, fall, and Grade 1-2 infusion related reactions. These adverse events were selected based on prevalence, previous evidence of their impact on cost and utility values and/or because they are unique to the mAbs as reported in clinical trials. We assumed that all ARIA events were mild-to-moderate symptomatic, requiring monthly MRIs accompanied by a follow-up office visit until resolution.²⁵⁻²⁷ The analysis further assumed that all ARIA events resolved in 12 weeks, resulting in 3 office visits and 3 MRI scans.²⁵⁻²⁷ Headaches in patients were assumed to be mild or moderate, which can be resolved with acute pain medications recommended for migraine, such as NSAIDs or acetaminophen.²⁸ Falls were assumed to cause mild injury and incur a one-time physician's office visit.²⁹ Infusion related reaction (IRR) was assumed to be either Grade 1 or Grade 2 which are typically managed via acute antihistamine or analgesic prescriptions without requiring a physician consultation.³⁰

To reflect the costs from these AE's, we assumed that an IRR incurred an additional 30-minute-to-1-hour monitoring following the initial post-infusion monitoring period.^{25-27,31} In real-world settings, patients are typically advised to take oral antihistamines or pain medications such as NSAID or acetaminophen to manage IRR symptoms.³¹ We did not include the costs of medications as they are considered minor. The cost estimates of managing the adverse events were extracted from literature and the Center for Medicare & Medicaid Services (CMS).²⁸⁻³¹ The simulations did not consider the recurrence of adverse events.

2.6.4. Discontinuation Rate

Phase 3 clinical trials of the mAbs reported treatment discontinuation due to adverse events, voluntary withdrawal, and death. We only considered discontinuation due to adverse events.¹⁰⁻¹² Of note, we assumed that the discontinuation rates do not account for temporary dose suspensions resulting from ARIA events. [See *Methods 2.5.3 Adverse Events*] The discontinuation rates were reported as cumulative rates at the end of each trial period (e.g., 18 months). The simulation assumed that treatment discontinuations mostly occur during the first 6 months. Thus, the discontinuation rate was converted to weekly rates during the first 6 months and applied to the model. Patients who discontinued treatments anytime during the model time horizon were assumed to follow the same progression rate as SOC arm immediately following discontinuation of the mAbs. Patients were assumed to discontinue the mAbs once they reached Moderate AD, after which their AD continued to progress following the SOC trajectory.

2.6.5. Costs

The analysis accounted for partial or all costs from patient healthcare, care partner healthcare, patient non-healthcare, out-of-pocket, patient lost productivity, care partner lost productivity (for both community and institutional settings), and long-term care costs, depending on the perspective. [See *Table 2*] Patient healthcare costs represent the direct medical costs including medications, hospitalizations, emergency department visits, outpatient visits, and neuropsychological assessments. Caregiver healthcare costs include the same elements of medical costs as those of patients, except for neuropsychological assessments. Patient non-healthcare costs include costs incurred by dependent living accommodations, community services, consumable goods, and financial support.⁵³ and neuropsychological assessments Patient out-of-pocket costs include medical costs not covered by insurance for medications, hospitalization, outpatient services, and other healthcare services.³⁸

Patient productivity at each AD state was estimated by a weighted average of individual earnings in males and females aged 65 and older, based on the data from previous literature.³² Care partner lost productivity was estimated based on the average hours spent caring for AD patients^{33,34} and the average wage in the US at the time of this analysis.³⁵

The monthly cost of the mAbs was estimated using the wholesale acquisition cost (WAC) for the treatments.¹³⁻¹⁵ Appropriate bottle units and costs were applied according to the FDA-recommended dose titration schedule for the mAbs at the initiation of the therapies.¹⁶⁻¹⁸ Since all three AD treatments are administered via intravenous (IV) infusion, typically provided by healthcare professionals in a clinical setting, same administration cost per infusion was applied across the mAb arms. Assuming that the mAb arms received the treatments in an outpatient setting, drug administration cost was estimated using current procedural terminology (CPT) from the 2024 physician fee schedule published by CMS.³¹ Corresponding drug and administration costs for each mAb was applied for each cycle based on the recommended dosing schedule.¹⁶⁻¹⁸ Cost related to monitoring and adverse event managements were also applied into our model. All cost outcomes were reported in the 2024 Q4 USD using the Consumer Price Index (CPI) Inflation Calculator.^{36,37}

2.6.6. Health Care Related Quality of Life

Patient utility values and care partner disutility values were included in the simulation as appropriate for each perspective [See *Methods 2.1 Model Overview*]. Patient utility values varied by patient's AD state and residential setting (either community or institutional).^{33,34} Care partner disutility values were incorporated and varied according to the patient's AD state.³⁸

2.6.7. Mortality

AD is a progressive disease that ultimately leads to death. The death rate for each cycle was estimated by weighing AD-state-specific mortality risk into the age- and sex-specific background mortality to account for differential death rate in the population by the mean age and sex ratio.^{5,41} Background mortality risk was estimated using the 2022 US mortality data from Human Mortality Database.⁴¹

2.7. Model Output

The primary outcomes in our model were costs and quality-adjusted life expectancy (QALYs). The incremental cost-effectiveness ratio (ICER) was calculated to compare the

treatments to SOC. ICERs were rounded to the nearest hundred USD. Additional outcomes are presented in the supplemental appendix. These include the time to transition from MCI to each advanced AD state in each arm, estimated death in each AD state, estimated treatment discontinuation prior to reaching Moderate AD, and prevalence of adverse events prior to reaching Moderate AD in each treatment arm. [See *Supplemental Appendix - Supplemental Table 2-4*]

2.8. Key Assumptions

Table 3 summarizes the key assumptions.

2.9. Analyses

A 1-week cycle and 10-year time horizon were used for our analysis. Costs and health effects were discounted at 3.0%.⁴³ ICERs were calculated and compared across the four strategies accordingly to their QALY gain. The willingness-to-pay (WTP) threshold of \$150,000 (\$150K)/QALY and \$200,000 (\$200K)/QALY in USD were used to assess treatment value.⁴³ Net monetary benefit (NMB) for each treatment was obtained using the \$150K/QALY threshold and following equation:

$$\text{NMB} = (\text{QALY gain} \times \text{WTP}) - \text{Cost}$$

One-way sensitivity analyses were performed for each model input to visualize and compare the impact of each parameter variations to the ICER of each AD treatment. Each input values were varied by $\pm 20\%$ to assess their impact on ICER at lower and higher values. The results were displayed in tornado diagrams, with five most influential parameters ranked by their impact, displaying the highest impact at the top. Cost-effectiveness plane and acceptability curve (CEAC) were plotted by using probabilistic analysis with 10,000 iterations to show varying cost-effectiveness to different WTP thresholds. Furthermore, expected value of perfect information (EVPI) analysis was undertaken to estimate monetized value of precise evidence of outcomes around mAbs based on NMB using the following equation:⁴⁴

$$\text{EVPI} = |\text{Average Value of Maximum NMB between Compared Strategies at Each Trials} - \text{Maximum Value of Average NMB between Compared Strategies}| \times \text{Effective Population}$$

EVPI provides the potential value of reducing uncertainty or amount of investment justifiable toward further research around the cost-effectiveness of mAbs to inform research priorities and treatment-related decision-making. A broad range of WTP was considered for both CEAC and EVPI, ranging from \$0 to \$1,000,000.

Two scenario analyses were conducted to investigate the societal impact of mAbs in AD when 1) the treatment efficacies are more distinguished across the mAbs using the network meta-analysis evidence, and 2) when the drug pricing is reduced via discounts and rebates in the market. Results are provided in the *Supplemental Appendix*.

All analyses were conducted in R (v. 4.4.3) using a cost-effectiveness analysis package *dampack*⁴⁵ and Microsoft® Excel® (Version 2505 Build 16.0.18827.20102).

3. RESULTS

3.1. Progression Trajectories: SOC vs. Treatments

Figure 2 presents the extrapolated progression trajectories of the four strategy arms. The three mAb treatment arms showed delayed progression in CDR-SB score than the SOC arm, with aducanumab exhibiting faster progression and donanemab exhibiting the slowest progression. Incorporating the assumption of lost efficacy once reaching Moderate AD (CDR-SB ≥ 9.5), each mAb arm exhibited a transition in progression rate between the month 55 and 60. When comparing the number of months spent at each AD state across the four strategy arms, aducanumab postponed progression up to 10 months, lecanemab up to 14 months and donanemab up to 15 months, approximately. (*Figure 2.B.*)

3.2. Base Case Results

Base case results from both the health care sector and modified societal perspectives are presented in *Table 4*. From the health care sector perspective, the mAb arms showed QALY gain of 0.23 for aducanumab, 0.35 for lecanemab and 0.37 for donanemab compared to the SOC arm over the 10-year time horizon. The mAbs increased health care sector costs by \$55,400 for aducanumab, \$73,100 for lecanemab, and \$81,900 for donanemab. The SOC had higher NMB (\$438,900) than any mAbs. Among the mAbs, lecanemab had the highest (\$434,800) and

aducanumab has the lowest NMB (\$429,700). The superior QALY gain and the favorable costs per QALY gain in lecanemab and donanemab resulted dominance over aducanumab. The comparative ICER in lecanemab versus the SOC was \$212,000/QALY and the ICER in donanemab compared to lecanemab was \$329,900/QALY.

From the modified societal perspective, the mAb arms had QALY gain of 0.25 for aducanumab, 0.37 for lecanemab and 0.40 for donanemab compared to the SOC arm. Addition of aducanumab in the treatment increased the societal costs by \$45,000, lecanemab increased it by \$54,000, and donanemab increased it by \$60,100 from the SOC costs. The NMB at \$200K/QALY threshold was the lowest in SOC (-\$151,100) and highest in lecanemab (-\$141,900). Aducanumab was also dominated by lecanemab from the societal perspective. The comparative ICER of adding lecanemab was \$175,300/QALY compared to SOC, and \$304,200/QALY for donanemab compared to the lecanemab.

3.3. One-Way Sensitivity Analyses

One-way sensitivity analyses were conducted to identify the top five key drivers of comparative cost-effectiveness for the pairwise strategy comparisons. The key drivers for higher ICERs were similar across the two perspectives (*Figure 3*). From the health care sector perspective, a higher ICER in lecanemab versus SOC was driven by an older patient age at a treatment initiation, a lower utility of patients with MCI or Mild AD in the community setting, a lower aducanumab acquisition cost and a higher lecanemab acquisition cost. A higher ICER in donanemab versus lecanemab was driven by a lower lecanemab acquisition cost, an older patient age at a treatment initiation, a lower discontinuation rate on donanemab, and a lower patient utility at Mild AD. From the modified societal perspective, an older age at treatment initiation, a lower patient utility at Mild AD, a lower aducanumab acquisition cost, and a higher lecanemab acquisition cost, and a lower productivity in care partners with patients with Severe AD were key drivers for higher ICER in lecanemab versus SOC. A higher ICER in donanemab versus lecanemab exhibited with an older age at treatment initiation, lower lecanemab acquisition cost, lower discontinuation rate in donanemab arm, a higher donanemab acquisition cost, and a lower patient quality of life at Mild AD.

3.4. Probabilistic Sensitivity Analysis

The probability of cost-effectiveness for all four strategies in lecanemab and donanemab was assessed through simulation using 10,000 iterations (*Figure 4*). Aducanumab was excluded from this analysis, because it was dominated by lecanemab and donanemab that had lower costs per QALY gain than aducanumab. From the health care sector perspective, lecanemab was 10.6% and 62.2% likely to be cost-effective compared to SOC under the \$150K/QALY and \$200K/QALY thresholds, respectively. Donanemab was 31.5% and 37.1% likely to be cost-effective compared to lecanemab under the \$150K/QALY and \$200K/QALY thresholds, respectively. From the modified societal perspective, lecanemab was 44.9% and 90.3% likely to be cost-effective compared to SOC under \$150K/QALY and \$200K/QALY thresholds, respectively. Donanemab was 33.4% and 39.3% likely to be cost-effective at the \$150K/QALY and \$200K/QALY thresholds respectively.

From the modified societal perspective, lecanemab was 44.9% and 90.3% likely to be cost-effective compared to SOC under \$150K/QALY and \$200K/QALY thresholds, respectively. Donanemab was 33.4% and 39.3% likely to be under \$150K/QALY and \$200K/QALY thresholds respectively.

When comparing all four strategies, the distribution of cost-effectiveness probabilities showed that SOC is most likely to be preferred at \$150K/QALY (*Figure 5*) from both the health care sector and the modified societal perspectives. Lecanemab had a higher probability of cost-effectiveness than SOC at approximately \$250K/QALY threshold for the health care sector perspective and \$200K/QALY threshold for the modified societal perspective. Donanemab maintained a higher probability of cost-effectiveness than SOC and lecanemab at approximately \$300K/QALY and higher thresholds for both perspectives.

3.5. Expected Value of Perfect Information

Figure 6 illustrates the estimated expected value of perfect information (EVPI) across the range of WTP thresholds between \$0 and \$1,000K/QALY. The EVPI for the decision to add lecanemab to the SOC peaked at a WTP of \$190K/QALY for the health care sector perspective and \$155K/QALY for the modified societal perspective, with the cost estimated to be worth as much as \$143 million. In contrast, the EVPI for the decision around donanemab and lecanemab

was worth as much as \$109 million approximately at the WTP of \$300K/QALY and \$275K/QALY for the healthcare sector and the modified societal perspectives, respectively. The EVPI around donanemab versus lecanemab gradually declined to zero toward the \$1,000K/QALY WTP threshold.

3.6. Model Validation

Cost-effectiveness estimates of mAbs in the current literature widely vary, primarily due to heterogeneity in models' parameter values, structural assumptions, and different interpretations of disease progression and health benefits from the interventions. To assess its external validity, this model's modified societal perspective results were compared with published cost-effectiveness analysis studies of one or more mAbs in AD.^{39,40,47-50}

In the current literature, costs and QALYs for supportive care or SOC in AD have been reported in the range of \$419,000 – \$670,000 and 2.89 – 4.95 from societal perspectives. The QALYs reported for SOC from our analysis fell within the range of the established estimates, whereas the costs were estimated to be higher than previously reported. This difference was expected as our model accounts for inflation and includes additional costs associated with the adverse events from the mAbs. Our analysis reports the incremental costs of \$49,000, \$64,800, and \$73,400 for aducanumab, lecanemab, and donanemab, respectively from the modified societal perspective. These figures are generally lower than the incremental costs reported in the past literature, which ranged from \$127,800 to \$202,000 for aducanumab³⁹, approximately \$120,000 for lecanemab^{40,49}, and from \$61,000 to \$71,600 for donanemab.^{47,48} This difference is largely attributed to model assumptions that incurred overall higher discontinuation rates and higher 12-week-long dose suspension rates from ARIA during the first 6 months, saving substantial drug costs in the cohort with MCI and Mild AD. [See *Supplemental Table 2-4*] While economic outcomes remain heterogeneous across studies, our findings align with the reported range of QALY estimates, supporting the credibility of our results.

4. DISCUSSION

This Markov model-based economic analysis estimated and compared the cost-effectiveness of adding the three FDA-approved mAbs to the current SOC in AD population. Aducanumab and donanemab were less likely to be cost-effective than lecanemab from both the health care sector and the modified societal perspectives. Lecanemab was only likely to be a considerable treatment option at a WTP threshold of \$200K/QALY from the societal perspective. None of the mAbs were found to be cost-effective at the traditional WTP threshold of \$150K/QALY. The key drivers that impact ICERs of the mAbs were the age at which the treatment was initiated, patient health state utility values associated with their AD state, and the drug acquisition costs. The EVPI for decisions involving the AD treatment strategies was estimated to be worth as much as \$143 million for lecanemab versus SOC, and \$109 million for donanemab versus lecanemab.

In the current US market, where Aduhelm, the branded aducanumab, has been withdrawn by the manufacturer, lecanemab and donanemab would be the only available mAbs for early AD patients. Given our analysis results using WAC, lecanemab would be considered the preferred option over donanemab. However, it is important to account for the potential net prices of these mAbs, which are their actual acquisition costs after manufacturer rebates and discounts. Given the lack of transparency around net prices in the US payer system, the true cost-effectiveness of lecanemab and donanemab may differ from the estimates of this research. The variability of cost-effectiveness of the mAbs was further explored in *Scenario Analysis 2* of the Supplemental Appendix.

When compared with current literature, our analysis reported generally higher QALY gain and lower incremental costs for each treatment arm. For instance, a lifetime model by Ross et al. reported that aducanumab increased lifetime QALYs by 0.133 and lifetime cost by \$127,800, and donanemab increased QALYs by 0.408 and cost by \$71,600 from the societal perspective.⁴⁸ In contrast, our model estimated that aducanumab, lecanemab, and donanemab increased the 10-year QALYs by 0.25, 0.37, and 0.40, and the costs by \$48,400, \$64,800, and \$73,400, respectively. These discrepancies are likely due to the shorter time horizon (10-year vs. lifetime), a higher survival from the lower baseline age (Baseline age: 71.1 vs. 75.2), and higher proportion of patients discontinued the treatment in our simulation. Ross and colleagues reported

that 50% of the patient died at 4.4 years in their simulation.⁴⁸ Our model projected 50% survival of AD patients at 8.2 years. The higher survival led to higher QALY and higher total cost in SOC. However, as our analysis assumed that patients discontinue therapy once developing Moderate AD, incremental costs from the mAbs were not as high as expected. The simulated cohort received the mAbs as short as 49 months (aducanumab) and up to 64 months (donanemab). Moreover, 14 – 20% of the simulated cohort discontinued the treatment prior to reaching Moderate AD. [See *Supplemental Table 2-4*]

This analysis is one of the first models to include all three mAbs indicated for early AD and assess the comparative cost-effectiveness of the mAbs in early AD patients. Besides the heterogeneities between this model and the published models, what makes this model valuable is the utilization of a continuous, unidirectional progression curve in CDR-SB score to map the clinical AD progression and capture the granular cost and health outcomes in the weekly cycle. Furthermore, this simulation incorporated adverse events such as headache, fall, and IRR, which raise concerns and hesitancy with increased burden in using mAbs among elderly patients with early AD. Additionally, owing to the fact that there could be various forms of caregiving and supporting AD patients, it is challenging to accurately capture health effects in AD using a simulation model which then potentially delay policymaking decisions. Addressing these evidence gaps is imperative to improve the accuracy of economic evaluations in AD.

This study discusses the cost effectiveness and the value of the three novel AD treatments from the health care sector and the modified societal perspectives in the US. Results from this research allude to health economic challenges and opportunities associated with the novel AD treatment for early AD patients. Findings from this research highlight that while these treatments, especially lecanemab, may offer somewhat cost-effective clinical benefit with an ICER under the WTP of \$200,000 per QALY gain, the usability of these treatments may only pertain to certain AD population. This raises questions about their long-term value in society. Additionally, the substantial financial burden potentiated from these mAbs requires careful consideration in promoting accessibility to the AD treatments. The results also stress the importance in exploring value-based pricing models and potential price adjustments to align these treatments with acceptable economic thresholds, ensuring access and sustainability of these treatments to patients with early AD. [See *Scenario Analysis 2*] These findings not only inform policy and financial strategies for stakeholders but also underscores the need for further research on indirect costs that

are associated with AD management, treatments, productivity impacts, and stakeholder-specific outcomes to refine the economic evaluation of these novel therapies.

There are several limitations to this study: 1) disease-associated costs and utility sourced from evidence published more than a decade ago may not be reflective of that in current AD population, 2) absence in post-marketing data may not accurately capture clinical outcomes in real-world setting, 3) this model assumed low-grade severity on all adverse events, not incurring any hospitalization, and 4) the modified societal perspective was not designed to capture certain indirect costs, such as transportation expenses. Due to these limitations, additional validation may be required to assess the accuracy of this analysis.

5. Conclusion

Findings from this analysis suggest that lecanemab may be cost-effective under the \$200,000/QALY benchmark at the published WAC in the US, while neither aducanumab nor donanemab would be cost-effective. Of note, the actual net prices paid by CMS for these drugs are likely to be substantially lower than the WAC. With aducanumab's withdrawal from the US market, enhancing clinical evidence and adjustments in drug pricing between the manufacturers and health care entities would improve cost-effectiveness and utilization of the mAbs among the early AD population in the US health care system. Additional research to close gaps in clinical evidence in the real-world population is warranted to improve accuracy of comparative economic evaluation in AD treatments.

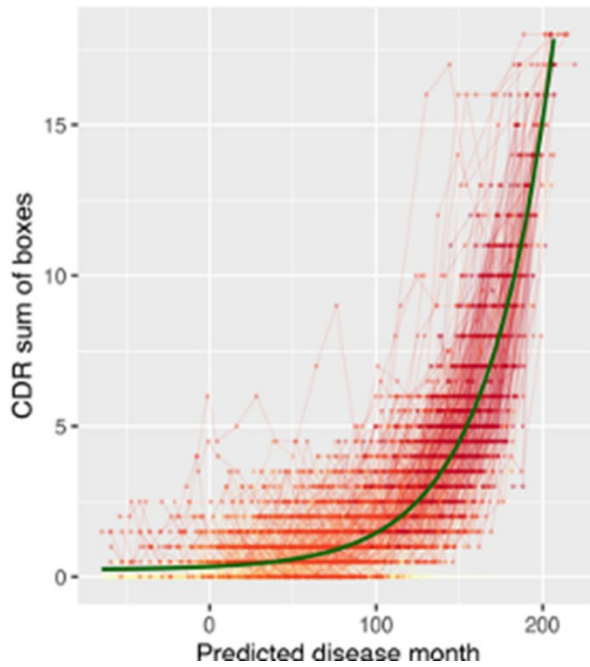
6. FIGURES AND TABLES

Table 1. AD Health States by Clinical Dementia Rating – Sum of Boxes (CDR-SB)⁴

AD Health States by CDR-SB	
Parameter	CDR-SB Range
Mild Cognitive Impairment (MCI)	0.5 – 4.0
Mild AD	4.5 – 9.0
Moderate AD	9.5 – 15.5
Severe AD	16.0 - 18.0

Figure 1. Progression Trajectory (A) Curve and (B) Formula of MCDP Model Developed by Kühnel et al.²²

(A)



(B)

$$\mu(t) = l \cdot \exp\left(\frac{t}{\exp(g)}\right) + v$$

g = scaling of time

v = mean score of cognitively normal individuals

l = mean deviation from v at time $t=0$

Table 2. Model Inputs

Model Parameters		Estimates			PSA Distribution	References
Baseline Age	71.1				Uniform	Assumption
Male%	45.9				Uniform	Assumption, 10-12
Baseline CDR-SB	3.3				Uniform	Assumption, 10-12
	Alzheimer's Disease (AD) States					
	MCI-AD	Mild AD	Moderate AD	Severe AD		
Cost per month						
Patient Healthcare	\$1,261	\$1,479	\$1,963	\$2,254	Gamma	34, 37, 53
Patient Non-Healthcare	\$223	\$412	\$654	\$1,098	Gamma	34, 37, 53
Caregiver Healthcare	\$757	\$785	\$801	\$813	Gamma	34, 37, 53
Patient Out-of-Pocket	\$184	\$184	\$184	\$184	Gamma	37, 38
Patient Productivity [†]	\$2,262	\$1,398	\$792	\$0	Gamma	32, 37
Caregiver Lost Productivity [‡]						
Community	\$2,479	\$4,060	\$4,527	\$10,707	Gamma	33-35
Institutionalized	\$1,078	\$1,797	\$2,659	\$4,707	Gamma	33-35
Long Term Care	\$9,277	\$9,277	\$9,277	\$9,277	Gamma	37, 54
Utility						
Patient Utility						
Community	0.73	0.69	0.53	0.38	Beta	34, 35
Institutionalized	0.73	0.71	0.48	0.31	Beta	34, 35
Caregiver Disutility	0.03	0.05	0.08	0.1	Beta	32
Other Inputs (per month)						
Institutionalization	1.7	4.3	11.6	43.2	Beta	55, 56
Mortality Risk due to AD	1.04	2.36	2.75	8.04	Normal	5, 6
	Treatment Options					
	Aducanumab	Lecanemab	Donanemab			
Drug Efficacy Parameters						
Primary Endpoint Reduction in Progression	22%	27%	29%			6, 10-12
Primary Endpoint	18 months	18 months	17.5 months			
D/C Rate at Primary Endpoint	10.0%	9.1%	6.9%			
Drug-Related Cost						
Drug Costs per month	\$2,717.40	\$2,304.74	\$2,780.20		Gamma	35, 36, 42
Administration Cost per month (CPT 96365)	\$57.70	\$115.40	\$57.40		Gamma	54, 31
MRI Cost (CPT 70553)		\$314.08			Gamma	31; [See <i>Supplemental Table 5</i> for schedule]
Adverse Events						

ARIA Rate per month	1.35%	0.89%	0.94%	Beta	
Management Cost per event [§]		\$1,209.10		Gamma	10-12, 31, 42
Disutility per event		0.14		Beta	
Headache Rate per month	1.12%	0.62%	0.80%	Beta	
Management Cost per event [§]		\$19.22		Gamma	10-12, 42
Disutility per event		0.14		Beta	
Fall Rate per month	0.81%	0.58%	0.76%	Beta	
Management Cost per event [§]		\$88.95		Gamma	10-12, 31, 58
Disutility per event		0.2		Beta	
IRR Rate per month	0.17%	1.50%	0.50%	Beta	
Management Cost per event [§]		\$20.41		Gamma	10-12, 25, 26, 31, 59
Disutility per event		0.011		Beta	
Discontinuation Rate per month	9.10%	6.90%	13.10%	Beta	10-12

AD, Alzheimer's Disease; ARIA, Amyloid Related Imaging Abnormality; D/C, Discontinuation; IRR, Infusion Related Reaction; MCI, Mild Cognitive Impairment;
All dollar amounts are in 2024 US dollar³⁷; Adverse events and discontinuations were assumed to occur during the first 6 month of treatment initiation. Disutility rates for adverse events were assumed per event.
†Patient productivity was estimated using weighted average of individual income among males and females aged 65 or older³²
‡Caregiver productivity was calculated using estimated hours lost per week and average hourly wage in the US (\$35.93; Jan 2025)(35).
§Adverse Event Management Costs were calculated as following: ARIA: monthly MRI and physician's office visit for 3 months; headache: outpatient prescription for migraine; Fall: a physician's office visit; IRR: additional 30-minutes-to-1-hour monitoring following initial monitoring (CPT 96366).

Table 3. Key Model Assumptions

Key Model Assumptions:
Patients did not improve, and the progression was unidirectional. (See <i>Figure 2</i>)
Costs and utility values were applied according to AD stages, as such data mapped by CDR-SB score was limited.
Progression trajectories for the treatment arms followed a similar trajectory as the progression in the SOC arm as measured by CDR-SB.
Treatment benefits were extrapolated until patients reach moderate or severe disease (CDR-SB ≥ 9.5)
Once patients entered Moderate AD, mAb treatments were discontinued
The discount rate for costs and outcomes was 3%.
Majority of adverse events and treatment discontinuation occurred in the first 6 months of trials
Once patients discontinued the treatment, their disease progression followed the same trajectory as the SOC.
The mAbs did not cost more than their wholesale acquisition cost
All patients with moderate, symptomatic ARIA discontinued the mAbs and underwent MRI monitoring every month for 12 weeks.
All IRR events were mild-to-moderate and lasted 24 hours. Disutility from IRR was equivalent to that of an injection site reaction. ⁵¹

Figure 2. (A) Progression Trajectory Curve in CDR-SB and (B) Transition Months to Each AD State

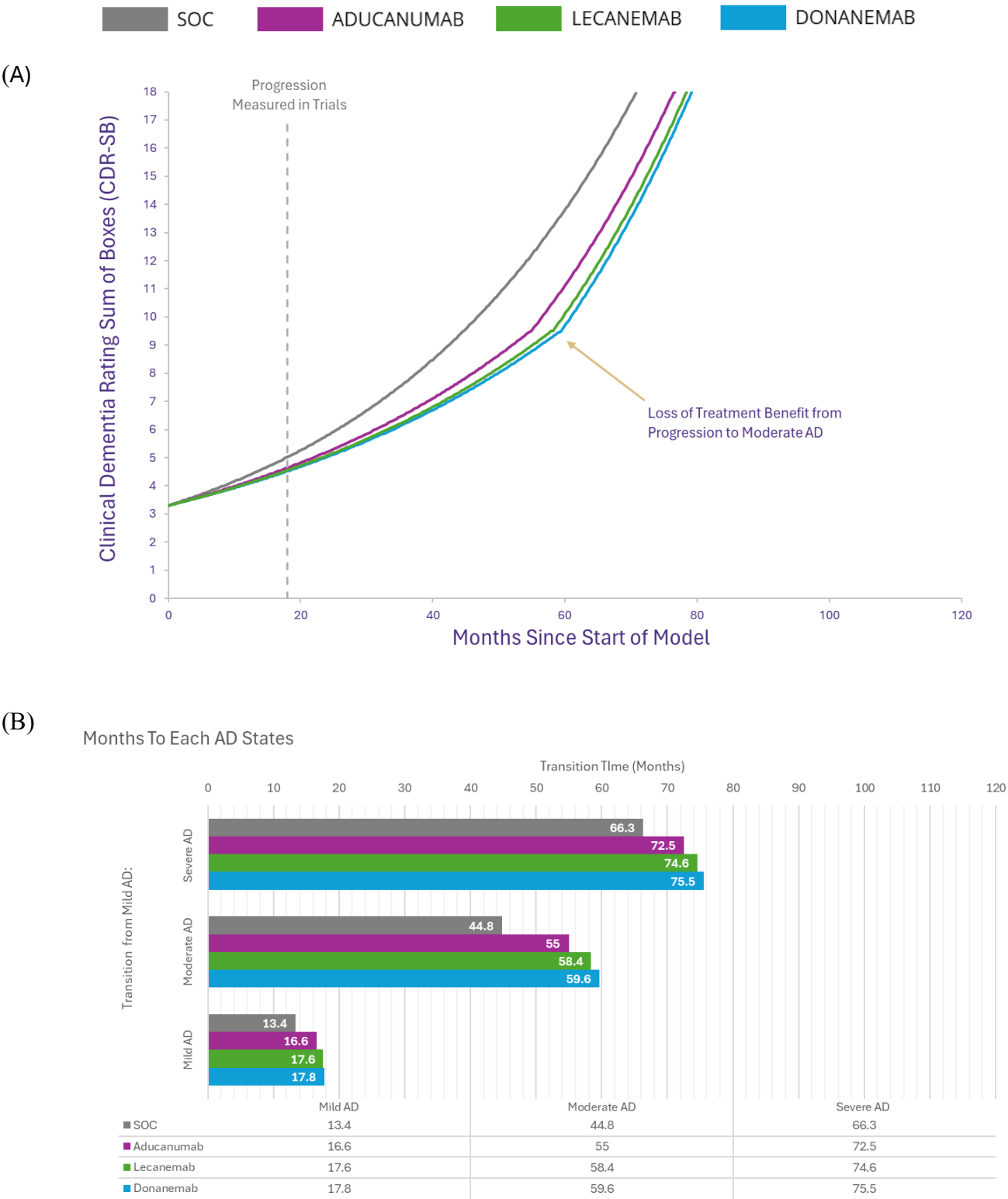
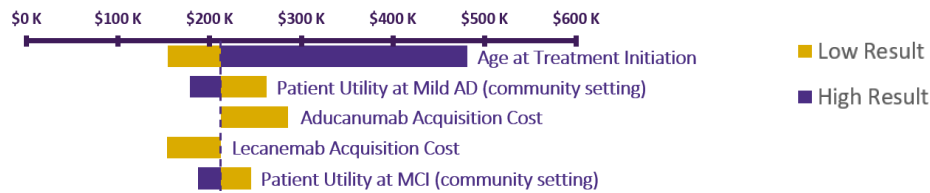


Table 4. Base Case Results for the Health Care Sector Perspectives and the Modified Societal Perspectives; Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-years; SOC, standarad of care; QALY, quality-adjusted life years

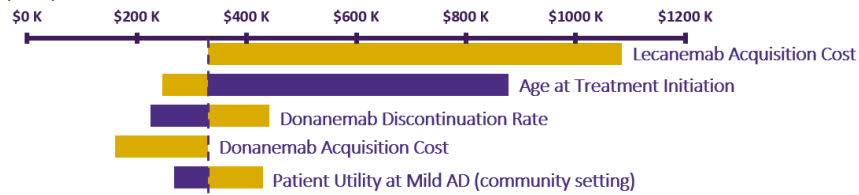
Treatment Cost		Costs	QALY	LYs	NMB	ICER vs. SOC	League ICER
<i>Health Care Sector Perspective</i>							
SOC	\$0	\$243,300	3.41	6.55	\$268,200	--	--
Aducanumab	\$80,327	\$298,700	3.64	6.78	\$247,300	\$239,600	Ext. Dom.
Lecanemab	\$105,500	\$316,400	3.76	6.85	\$247,600	\$212,000	\$212,000
Donanemab	\$116,400	\$325,200	3.78	6.88	\$241,800	\$220,400	\$329,900
<i>Modified Societal Perspective</i>							
SOC	\$0	\$757,800	3.03	6.55	-\$303,300	--	--
Aducanumab	\$80,327	\$806,200	3.28	6.78	-\$314,200	\$193,100	Ext. Dom.
Lecanemab	\$105,500	\$822,700	3.40	6.85	-\$312,700	\$175,300	\$175,300
Donanemab	\$116,400	\$831,200	3.43	6.88	-\$316,700	\$184,400	\$304,200

Figure 3. One-Way Sensitivity Analysis Results from (A) the Health Care Sector Perspective and (B) the Modified Societal Perspective: (1) Lecanemab vs. SOC, and (2) Donanemab vs. Lecanemab

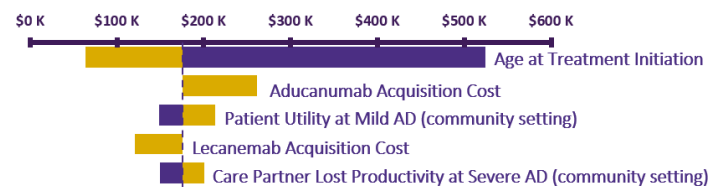
(A1)



(A2)



(B1)



(B2)

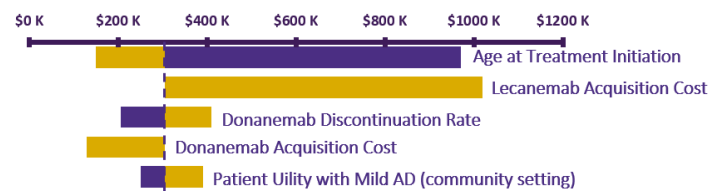
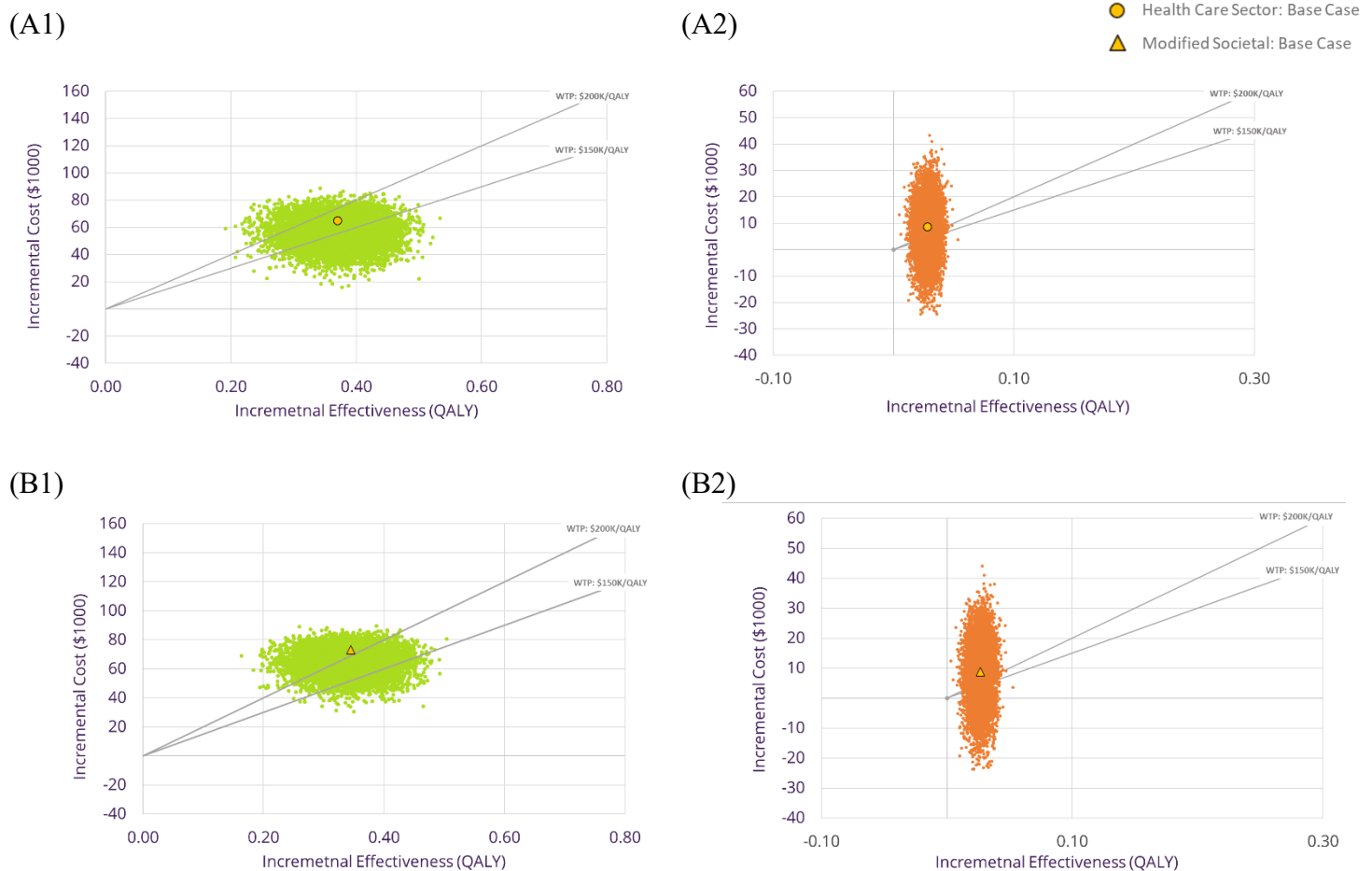


Figure 4. Probabilistic Sensitivity Analysis: Cost-Effectiveness (CE) Plane Results for (A) the Health Care Sector Perspective and (B) the Modified Societal Perspective with (C) Probability Distribution Table: (1) Lecanemab vs. SOC, and (2) Donanemab vs. Lecanemab. Cost-Effectiveness Probabilities by \$150K/QALY and \$200K/QALY WTP Thresholds.



Health Care Sector Perspective			Modified Societal Perspective		
WTP Threshold	Lecanemab vs. SOC	Donanemab vs. Lecanemab	WTP Threshold	Lecanemab vs. SOC	Donanemab vs. Lecanemab
ICER $\leq$ \$150K/QALY	10.6%	31.5%	ICER $\leq$ \$150K/QALY	44.9%	33.4%
ICER $\leq$ \$200K/QALY	62.2%	37.1%	ICER $\leq$ \$200K/QALY	90.3%	39.3%

Figure 5. Cost-Effectiveness Acceptability Curve for (A) the Health Care Sector Perspective and (B) the Modified Societal Perspective

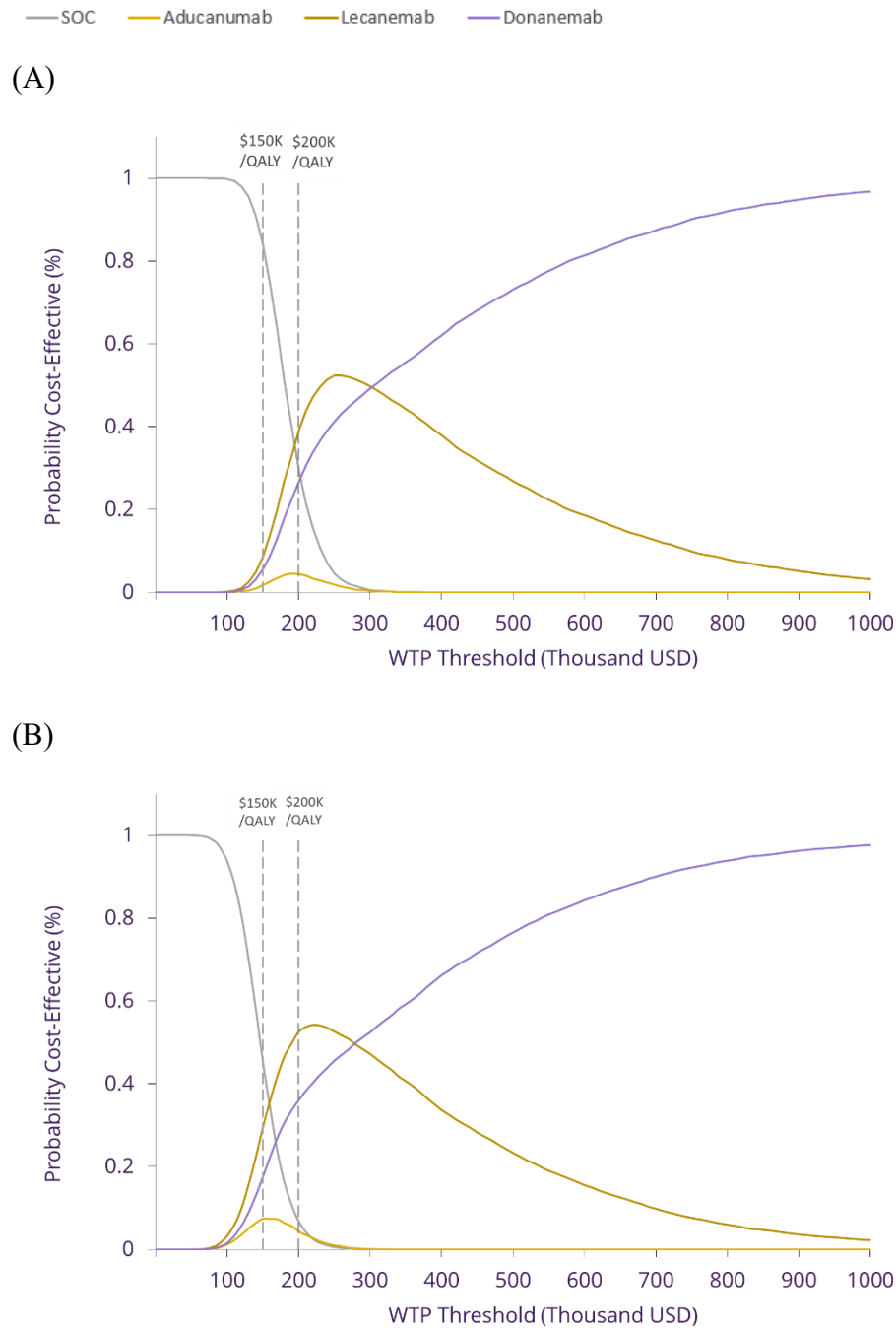
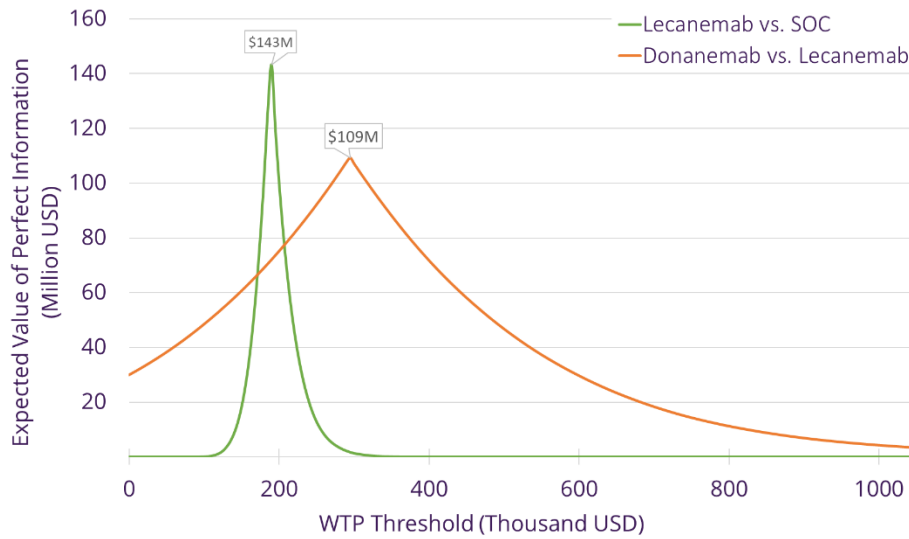
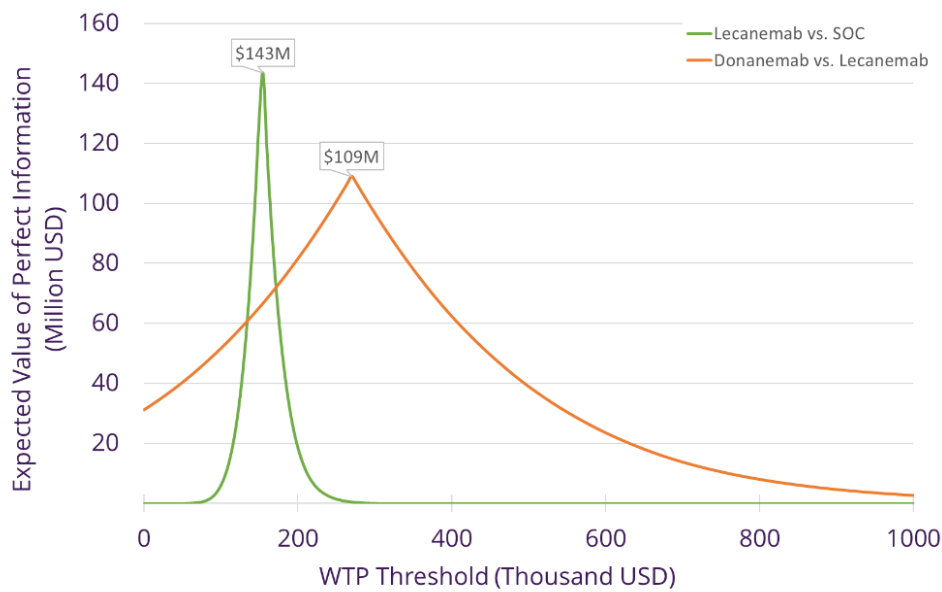


Figure 6. Expected Value of Information for (A) the Health Care Sector Perspective and (B) the Modified Societal Perspective

(A)



(B)



7. REFERENCES

1. Alzheimers Dement. *2024 Alzheimer's Disease facts and figures*. 2024 May;20(5):3708-3821. doi: 10.1002/alz.13809. Epub 2024 Apr 30.
2. Wolk, DA. Clinical features and diagnosis of Alzheimer disease. UpToDate. UpToDate; 2024. Accessed 20 October, 2024.
3. Alzheimers Dement. *2025 Alzheimer's disease facts and figures*. 2025 Apr 29;21(4):e70235. doi: 10.1002/alz.70235. PMCID: PMC12040760.
4. O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, Lupo PJ, Reisch JS, Doody R; Texas Alzheimer's Research Consortium. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. *Arch Neurol*. 2008 Aug;65(8):1091-5.
5. Crowell V, Reyes A, Zhou SQ, Vassilaki M, Gsteiger S, Gustavsson A. Disease severity and mortality in Alzheimer's disease: an analysis using the U.S. National Alzheimer's Coordinating Center Uniform Data Set. *BMC Neurol*. 2023;23(1):302. Published 2023 Aug 14. doi:10.1186/s12883-023-03353-w
6. Andersen K, Nielsen H, Lolk A, Andersen J, Becker I, Kragh-Sørensen P. Incidence of very mild to severe dementia and Alzheimer's disease in Denmark: the Odense Study. *Neurology*. 1999;52(1):85-90. doi:10.1212/wnl.52.1.85
7. FDA Grants Accelerated Approval for Alzheimer's Drug. FDA. 2021. <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug>
8. FDA approves treatment for adults with Alzheimer's disease. U.S. Food & Drug Administration, 02 Jul. 2024. Accessed 16 Oct. 2024. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease#:~:text=The%20U.S.%20Food%20and%20Drug,studied%20in%20the%20clinical%20trials>.
9. FDA Grants Accelerated Approval for Alzheimer's Disease Treatment. U.S. Food & Drug Administration, 06 Jan. 2023, <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment>. Accessed 16 Oct. 2024.
10. Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, Dent G, Hansson O, Harrison K, von Hehn C, Iwatsubo T, Mallinckrodt C, Mummery CJ, Muralidharan KK, Nestorov I, Nisenbaum L, Rajagovindan R, Skordos L, Tian Y, van Dyck CH, Vellas B, Wu S, Zhu Y, Sandrock A. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *J Prev Alzheimers Dis*. 2022;9(2):197-210.

11. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM; TRAILBLAZER-ALZ 2 Investigators. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023 Aug 8;330(6):512-527.
12. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023 Jan 5;388(1):9-21.
13. Product Name. Aduhelm. RED BOOK Online. IBM Micromedex [database online]. Merative; 2024. Accessed 21 November, 2024. <https://www.micromedexsolutions.com>.
14. Product Name. Kinsula. RED BOOK Online. IBM Micromedex [database online]. Merative; 2024. Accessed 21 November, 2024. <https://www.micromedexsolutions.com>
15. Product Name. Leqembi. RED BOOK Online. IBM Micromedex [database online]. Merative; 2024. Accessed 21 November, 2024. <https://www.micromedexsolutions.com>
16. Aduhelm (aducanumab) [Package Insert]. Cambridge, MA: Biogen and Eisai; 2021.
17. Leqembi (lecanemab) [Package Insert]. Nu Iey, NJ: Eisai, Inc. and Biogen; 2023.
18. Kinsula (donanemab) [Package Insert]. Indianapolis, IN: Eli Lilly and Company; 2024.
19. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. *Value Health*. 2022;25(1):3-9.
doi:10.1016/j.jval.2021.11.1351
20. Bloudek, Lisa, David Elsea, Ashley Kang, Sean D. Sullivan and Peter Neumann. Simulation Model of Slowing Progression in Alzheimer's Disease: Technical Report. Curta, 20 December, 2023.
21. Social Security Administration. *Medicare*. 2025 January. Accessed on May 1st, 2025. <https://www.ssa.gov/pubs/EN-05-10043.pdf>
22. Kühnel L, Berger AK, Markussen B, Raket LL. Simultaneous modeling of Alzheimer's disease progression via multiple cognitive scales. *Stat Med*. Jun 30 2021;40(14):3251-3266.
doi:10.1002/sim.8932
23. Epstein NU, Saykin AJ, Risacher SL, Gao S, Farlow MR; Alzheimer's Disease Neuroimaging Initiative (ADNI). Differences in medication use in the Alzheimer's disease neuroimaging initiative: analysis of baseline characteristics. *Drugs Aging*. 2010;27(8):677-686. doi:10.2165/11538260-000000000-00000

24. Terao I, Kodama W. Comparative efficacy, tolerability and acceptability of donanemab, lecanemab, aducanumab and lithium on cognitive function in mild cognitive impairment and Alzheimer's disease: A systematic review and network meta-analysis. *Ageing Res Rev.* 2024;94:102203. doi:10.1016/j.arr.2024.102203
25. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate Use Recommendations. *J Prev Alzheimers Dis.* 2021;8(4):398-410. doi:10.14283/jpad.2021.41
26. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362-377. doi:10.14283/jpad.2023.30
27. Rabinovici GD, Selkoe DJ, Schindler SE, et al. Donanemab: Appropriate use recommendations. *J Prev Alzheimers Dis.* 2025;12(5):100150. doi:10.1016/j.tjpad.2025.100150
28. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. *Nat Rev Neurol.* 2021;17(8):501-514. doi:10.1038/s41582-021-00509-5
29. Epstein NU, Guo R, Farlow MR, Singh JP, Fisher M. Medication for Alzheimer's disease and associated fall hazard: a retrospective cohort study from the Alzheimer's Disease Neuroimaging Initiative. *Drugs Aging.* 2014;31(2):125-129. doi:10.1007/s40266-013-0143-3
30. Barroso A, Estevinho F, Hespanhol V, Teixeira E, Ramalho-Carvalho J, Araújo A. Management of infusion-related reactions in cancer therapy: strategies and challenges. *ESMO Open.* 2024;9(3):102922. doi:10.1016/j.esmoop.2024.102922
31. Search the Physician Fee Schedule, CMS.gov. Last updated 04/01/2025. Accessed 05/04/2025. <https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=4&HT=0&CT=3&H1=96360&M=5>
32. Prados MJ, Liu Y, Jun H, Lam J, Mattke S. Projecting the long-term societal value of a disease-modifying treatment for Alzheimer's disease in the United States. *Alzheimers Dement.* Jan 2022;18(1):142-151. doi:10.1002/alz.12578 [Technical Appendix]
33. Neumann PJ, Kuntz KM, Leon J, et al. Health utilities in Alzheimer's disease: a cross-sectional study of patients and caregivers. *Med Care.* Jan 1999;37(1):27-32. doi:10.1097/00005650-199901000-00005
34. Neumann PJ, Hermann RC, Kuntz KM, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology.* Apr 12 1999;52(6):1138-45. doi:10.1212/wnl.52.6.1138

35. United States Bureau of Labor Statistics. Table B-3. Average hourly and weekly earnings of all employees on private nonfarm payrolls by industry sector, seasonally adjusted. Accessed 04 May 2025. <https://www.bls.gov/news.release/empst.t19.htm>.
36. Institute For Clinical and Economic Value. ICER's Reference Case for Economic Evaluations: Elements and Rationale. 2024. September 30. <https://icer.org/wp-content/uploads/2024/02/Reference-Case-4.3.25.pdf>
37. CPI Inflation Calculator. U.S. Bureau of Labor Statistics. Accessed April 20, 2025. https://www.bls.gov/data/inflation_calculator.htm
38. Oney, M., White, L., & Coe, N. B. (2022). Out-of-pocket costs attributable to dementia: A longitudinal analysis. *Journal of the American Geriatrics Society*, 70(5), 1538–1545. <https://doi.org/10.1111/jgs.17746>
39. Institute For Clinical and Economic Value. Aducanumab for Alzheimer's Disease:: Final Evidence Report and Meeting Summary. 2021. August 5. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf
40. Institute For Clinical and Economic Value. Lecanemab for Early Alzheimer's Disease: Final Evidence Report. 2023. April 17. https://icer.org/wp-content/uploads/2023/04/ICER_Alzheimers-Disease_Final-Report_For-Publication_04172023.pdf
41. Human Mortality Databases. 2024. <https://www.mortality.org/>
42. Sussman, M., Benner, J., Neumann, P., & Menzin, J. (2018). Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: Results from the US societal and payer perspectives. *Cephalalgia : an international journal of headache*, 38(10), 1644–1657. <https://doi.org/10.1177/0333102418796842>
43. Institute For Clinical and Economic Value. Value Assessment Framework. 2023. September 25. https://icer.org/wp-content/uploads/2023/10/ICER_2023_VAF_For-Publication_101723.pdf
44. Fenwick E, Steuten L, Knies S, et al. Value of Information Analysis for Research Decisions- An Introduction: Report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. *Value Health*. 2020;23(2):139-150. doi:10.1016/j.jval.2020.01.001
45. Alarid-Escudero F, Knowlton G, Easterly C, Enns E (2024). dampack: Decision-Analytic Modeling Package. R package version 1.0.2.1000, <https://CRAN.R-project.org/package=dampack>.
46. Terao I, Kodama W. Comparative efficacy, tolerability and acceptability of donanemab, lecanemab, aducanumab and lithium on cognitive function in mild cognitive impairment and Alzheimer's disease: A systematic review and network meta-analysis. *Ageing Res Rev*. 2024;94:102203. doi:10.1016/j.arr.2024.102203

47. Institute For Clinical and Economic Value. Beta-Amyloid Antibodies for Early Alzheimer's Disease: Draft Evidence Report 2022. December 22. https://icer.org/wp-content/uploads/2021/12/ICER_Alzheimers-Disease_Draft-Report_12222022-1.pdf
48. Ross EL, Weinberg MS, Arnold SE. Cost-effectiveness of Aducanumab and Donanemab for Early Alzheimer Disease in the US. *JAMA Neurol.* 2022;79(5):478-487. doi:10.1001/jamaneurol.2022.0315
49. Wright AC, Lin GA, Whittington MD, et al. The effectiveness and value of lecanemab for early Alzheimer disease: A summary from the Institute for Clinical and Economic Review's California Technology Assessment Forum. *J Manag Care Spec Pharm.* 2023;29(9):1078-1083. doi:10.18553/jmcp.2023.29.9.1078
50. Tahami Monfared AA, Tafazzoli A, Chavan A, Ye W, Zhang Q. The Potential Economic Value of Lecanemab in Patients with Early Alzheimer's Disease Using Simulation Modeling. *Neurol Ther.* 2022;11(3):1285-1307. doi:10.1007/s40120-022-00373-5
51. Walter E, Berger T, Bajer-Kornek B, Deisenhammer F. Cost-utility analysis of alemtuzumab in comparison with interferon beta, fingolimod, and natalizumab treatment for relapsing-remitting multiple sclerosis in Austria. *J Med Econ.* 2019;22(3):226-237. doi:10.1080/13696998.2018.1556668
52. Ito K, Chapman R, Pearson SD, Tafazzoli A, Yaffe K, Gurwitz JH. Evaluation of the Cost-effectiveness of Drug Treatment for Alzheimer Disease in a Simulation Model That Includes Caregiver and Societal Factors. *JAMA Netw Open.* Oct 1 2021;4(10):e2129392. doi:10.1001/jamanetworkopen.2021.29392
53. Robinson RL, Rentz DM, Andrews JS, et al. Costs of Early Stage Alzheimer's Disease in the United States: Cross-Sectional Analysis of a Prospective Cohort Study (GERAS-US)1. *J Alzheimers Dis.* 2020;75(2):437-450. doi:10.3233/JAD-191212
54. Nandi, A., Counts, N., Bröker, J., Malik, S., Chen, S., Han, R., Klusty, J., Seligman, B., Tortorice, D., Vigo, D., & Bloom, D. E. (2024). Cost of care for Alzheimer's disease and related dementias in the United States: 2016 to 2060. *npj aging*, 10(1), 13. <https://doi.org/10.1038/s41514-024-00136-6>
55. Davis M, O'Connell T, Johnson S, et al. Estimating Alzheimer's Disease Progression Rates from Normal Cognition Through Mild Cognitive Impairment and Stages of Dementia. *Current Alzheimer Research.* 2018-06-11 2018;15(8):777-788. doi:10.2174/1567205015666180119092427
56. Herring WL, Gould IG, Fillit H, et al. Predicted Lifetime Health Outcomes for Aducanumab in Patients with Early Alzheimer's Disease. *Neurology and Therapy.* 2021;10(2):919-940. doi:10.1007/s40120-021-00273-0

57. Centers for Disease Control and Prevention. (2021, September 10). FASTSTATS - body measurements. Centers for Disease Control and Prevention. Accessed March 10, 2025. <https://www.cdc.gov/nchs/fastats/body-measurements.htm>
58. Frick KD, Kung JY, Parrish JM, Narrett MJ. Evaluating the cost-effectiveness of fall prevention programs that reduce fall-related hip fractures in older adults. *J Am Geriatr Soc.* 2010;58(1):136-141. doi:10.1111/j.1532-5415.2009.02575.x
59. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ.* 2011;12(3):219-230. doi:10.1007/s10198-010-0224-8

8. SUPPLEMENTAL APPENDIX

Supplemental Table 1. Impact Inventory

Sector	Type of Impact (list category within each sector, with unit of measure if relevant) ^a	Included in This Health Impact Analysis From the Following Perspective?		Notes on Source of Evidence
		Health Care Sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects	✓	✓	
	Health-related quality-of-life effects	✓	✓	
	Other health effects (eg, adverse events and secondary transmissions of infections)	✓	✓	
	Medical costs			
	Paid for by third-party payers	✓	✓	
	Paid for by patients out-of-pocket	✓	✓	
	Future related medical costs (payers and patients)		✓	
Future unrelated medical costs (payers and patients)				
Informal Health Care Sector				
Health	Patient-time costs	NA	✓	See Footnote ^a
	Unpaid caregiver-time costs	NA	✓	
	Transportation costs	NA	*	
Non-Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	✓	
	Cost of unpaid lost productivity due to illness	NA	✓	
	Cost of uncompensated household production	NA	✓	
Consumption	Future consumption unrelated to health	NA	✓	
Social Services	Cost of social services as part of intervention	NA	*	See Footnote ^a
Legal or Criminal Justice	None	NA		
Education	None	NA		
Housing	None	NA		
Environment	None	NA		

a. Partially included under patient non-healthcare cost which include care-related transportation, nursing or home aids, and food delivery for patients;

Supplemental Table 2. Prevalence of Death by AD State

	(1) MCI	2. (1) + Mild AD	3. (2) + Moderate AD	4. (3) + Severe AD
SOC	1.6%	10.9%	18.7%	65.5%
Aducanumab	2.0%	13.6%	20.1%	63.2%
Lecanemab	2.2%	14.5%	20.6%	62.4%
Donanemab	2.2%	14.9%	20.9%	62.0%

Supplemental Table 3. Prevalence of Treatment Discontinuation by Treatment Arm Prior to Progression to Moderate AD

	MCI	MCI + Mild AD
Aducanumab	7.2%	14.4%
Lecanemab	5.6%	11.2%
Donanemab	10.4%	20.8%

Supplemental Table 4. Prevalence of Adverse Events by Treatment Arm During the First 6 Months Following Treatment Initiation

	ARIA	Fall	Headache	IRR
Aducanumab	21.1%	12.0%	16.5%	2.4%
Lecanemab	14.3%	8.8%	9.5%	22.4%
Donanemab	14.4%	11.1%	11.5%	7.2%

Supplemental Table 5. MRI Monitoring Schedule Recommendations

	<i>Aducanumab²⁵</i>	<i>Lecanemab²⁶</i>	<i>Donanemab²⁷</i>
Recommended MRI schedule after treatment initiation	<i>Prior to treatment initiation, prior to 5th, 7th, and 12th infusions.</i>	<i>Prior to treatment initiation, prior to 5th, 7th, and 14th infusions.</i>	<i>Prior to treatment initiation, prior to 2nd, 3rd, 4th, and 7th infusions.</i>
Recommended MRI schedule post-ARIA	<i>Monthly MRI until ARIA resolves</i>		

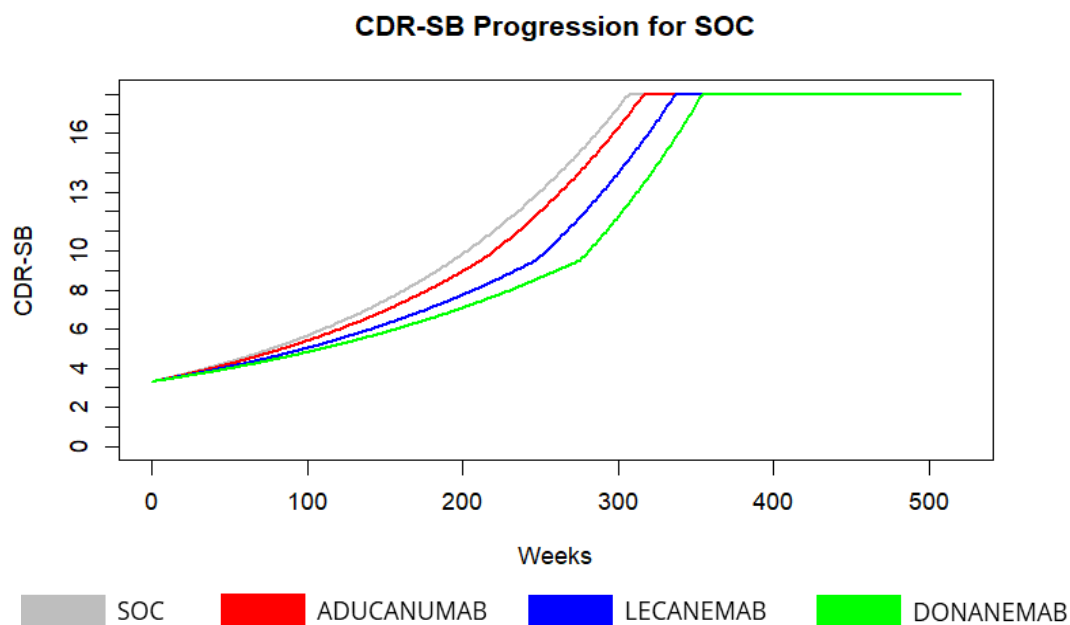
Scenario Analysis 1. Network Meta-Analysis from the Modified Societal Perspective

In the absence of head-to-head trials between the four strategies, economic evaluation using network meta-analysis (NMA) informs standardized estimates in relative treatment efficacy, allowing more accurate comparative cost-effectiveness analysis. A scenario analysis was conducted to assess impact on mAbs' cost-effectiveness from the modified societal perspective, using drug efficacy data derived from a peer-reviewed NMA. (46) The NMA evaluated the relative efficacy of aducanumab, lecanemab, donanemab, and lithium compared to conventional SOC. The treatment efficacy inputs used in the base case analysis and those based on the NMA are presented in panel (*Table 1*), and visual representation of extrapolated AD progression using the NMA data is shown in panel (*Figure 1*), and the analysis results are presented in panel (*Table 2*).

SA1.Table 1. Treatment Efficacy Inputs from the Referenced NMA

	Aducanumab	Lecanemab	Donanemab	Source
Trial-based Percent Reduction in Progression	22.0%	27.11%	28.9%	46
NMA-based Percent Reduction in Progression	10.4%	25.5%	34.3%	
NMA: network meta-analysis				

SA1.Figure 1. AD Progression Extrapolation Based on the Referenced NMA



SA1.Table 2. Model Outcomes from the Modified Societal Perspective

	Costs	QALY	LYs	NMB	ICER vs. SOC	League ICER
SOC	\$757,800	3.03	6.55	-\$303,300	--	--
Aducanumab	\$815,700	3.10	6.64	-\$350,700	\$911,000	ED
Lecanemab	\$823,600	3.37	6.83	-\$318,100	\$195,800	ED
Donanemab	\$829,100	3.55	6.97	-\$296,600	\$138,300	\$138,300
ED: extended dominance; ICER: incremental cost-effectiveness ratio; Ly: life years; NMB: net monetary benefit; SOC: standard of care;						

Scenario Analysis 2. Discounted Drug Pricing from the Modified Societal Perspective

A separate scenario analysis was conducted to examine the potential impact of drug pricing discounts ranging from 10% to 50% from WAC from the modified societal perspective. Deterministic model inputs were used to perform each scenario analysis. The analysis result below presents cost-effectiveness profiles of the strategies identified from each discount scenario. The cost-effectiveness profile of SOC does not vary with drug price discounts, thus indicated at the top of the table below. The rightmost column presents the comparative ICER, which represents cost-effectiveness of each mAbs compared to preceding strategy, ranked in the increasing order of costs and QALYs. In each scenario, strategies that were dominated (D) or extendedly dominated (ED) were identified and excluded from the relative ICER calculation.

SA2.Table 1. Cost-Effectiveness Profile Under Varied Drug Price Discounts from the Modified Societal Perspective

	Costs	QALYs	LYs	NMB	ICER vs. SOC	Comparative ICER
SOC	\$757,800	3.03	6.55	-\$303,300	--	--
10% Discount on WAC						
	Costs	QALYs	LYs	NMB	ICER vs. SOC	Comparative ICER
Aducanumab	\$809,200	3.10	6.64	-\$344,200	\$807,800	ED
Lecanemab	\$813,700	3.37	6.83	-\$308,200	\$166,400	ED
Donanemab	\$817,300	3.55	6.97	-\$284,800	\$115,400	\$115,400
20% Discount on WAC						
	Costs	QALYs	LYs	NMB	ICER vs. SOC	Comparative ICER
Aducanumab	\$802,600	3.10	6.64	-\$337,600	\$704,500	ED
Lecanemab	\$803,900	3.37	6.83	-\$298,400	\$137,000	ED
Donanemab	\$805,500	3.55	6.97	-\$273,000	\$92,500	\$92,500
30% Discount on WAC						
	Costs	QALYs	LYs	NMB	ICER vs. SOC	Comparative ICER
Aducanumab	\$796,000	3.10	6.64	-\$331,000	\$601,200	ED
Lecanemab	\$794,000	3.37	6.83	-\$288,500	\$107,600	ED
Donanemab	\$793,700	3.55	6.97	-\$261,200	\$69,600	\$69,600
40% Discount on WAC						
	Costs	QALYs	LYs	NMB	ICER vs. SOC	Comparative ICER
Aducanumab	\$789,500	3.10	6.64	-\$324,500	\$497,900	D
Lecanemab	\$784,100	3.37	6.83	-\$278,600	\$78,100	D
Donanemab	\$781,900	3.55	6.97	-\$249,400	\$46,700	\$46,700
50% Discount on WAC						
	Costs	QALYs	LYs	NMB	ICER vs. SOC	Comparative ICER
Aducanumab	\$782,900	3.10	6.64	-\$317,900	\$394,700	D
Lecanemab	\$774,200	3.37	6.83	-\$268,700	\$48,700	D
Donanemab	\$770,100	3.55	6.97	-\$237,600	\$23,800	\$23,800
D: dominance; ED: extended dominance; ICER: incremental cost-effectiveness ratio; LYs: life years; NMB: net monetary benefit; mAbs: monoclonal antibodies; SOC: standard of care; WAC: wholesale acquisition cost;						