

## Understanding Payer Evidentiary Needs for Alzheimer's Disease Monoclonal Antibody Treatments

### Executive Summary

The Duke-Margolis Center for Health Policy, under a cooperative agreement with the US Food and Drug Administration (FDA), held a roundtable on July 14, 2021, to facilitate a discussion and exchange of ideas among participants about issues associated with use of Alzheimer's disease (AD) monoclonal antibodies (mAbs) that are important to the payer community.

This class of drugs includes but is not limited to aducanumab, which was recently granted accelerated approval (AA) by the FDA; there are additional mAbs in advanced clinical development that show preliminary evidence of plaque reductions in many AD patients. Stakeholders discussed views on key issues that payers are facing in making coverage and payment decisions involving the AD mAb drug class, including:

- Payers' activities to review the evidence relevant to these decisions,
- Top areas where further evidence is needed,
- Opportunities for improving the evidence base on mAb treatments for AD, and
- Potential steps for promoting equitable patient access in these efforts.

Stakeholder discussion was focused on the entire class of mAbs currently undergoing clinical trials that aim to slow the progression of AD, and also considered whether and how the recent aducanumab approval might impact evidence development for future AD therapeutics. While the accelerated approval of aducanumab relied upon results of a surrogate endpoint reduction of amyloid plaque, participants emphasized that the ultimate treatment goal of mAb AD drugs was their impact on cognitive and functional outcomes for patients. Some discussion focused on the strength of the evidence related to plaque reduction as a surrogate marker for cognitive improvement, based on the evidence that is currently publicly available.

In the initial discussion, payers generally noted the AA approval for AD as being impactful to a larger and more heterogeneous population than prior AA approvals in other disease areas with important unmet medical needs (e.g., oncology); therefore, based on both the potential scope of the population and the expected price per unit, payers expect coverage decisions to be more consequential. Some stakeholders noted that Medicare's usual Part B pricing rules, and similar private payment approaches for specialty drugs, would likely lead to substantial patient copays and pose a barrier to equitable access that has the potential to increase health disparities. Alternative payment approaches based on further postmarket evidence, population- rather than volume-based payments, or payments linked to outcomes might help address this challenge.

Presenters highlighted the high burden of Alzheimer's on millions of Americans, recognizing that although mAb treatments are not expected to be a cure, even incremental progress in modifying the course of AD is very important for a disease with no survivors. Some participants noted that early drugs with modest effects should be considered an essential building block for drugs and drug combinations that could keep improving. However, many stakeholders noted that pricing and payment will likely be a key issue for more rapid adoption and acceptance of these treatments as they become available, especially with payers expressing uncertainty about magnitude of benefits and extent of treatment use. They noted that if prices are high at the "incremental" stage, so that the drugs are inaccessible or too costly for many eligible patients, that trajectory flattens.

Stakeholders generally agreed that the National Coverage Analysis (NCA) underway at the Centers for Medicare and Medicaid Services (CMS), expected to reach a National Coverage Determination (NCD) for monoclonal antibodies directed against amyloid for the treatment of AD within the next nine months, would have a critical impact on coverage and access since 80% or more of the expected patient population for the mAbs are Medicare beneficiaries. Stakeholders noted that, until there is a NCD for aducanumab, some payers are considering coverage that corresponds to the patient populations and conditions in the clinical trial, while other payers are limiting coverage more tightly, have not yet made an initial determination, or have declared that they will not be covering the drug.

To adequately address stakeholders' concerns about appropriate coverage and use of new mAbs for AD, there was general agreement that manufacturers, clinicians, and payers could work together to augment the evidence base on the efficacy and safety of these drugs. This includes understanding how studies underway or planned can provide more evidence on class effects involving the mAbs, as well as how more real-world data (RWD) could help address important issues related to comparative effectiveness of potential mAb treatments, risks and benefits across subgroups, and supporting best practices for mAb use. CMS has an opportunity to support such data collection through establishing Coverage with Evidence Development (CED) as part of its NCD. However, some stakeholders emphasized that these postapproval studies may have difficulty resolving some questions unless it is feasible to conduct randomization, and others cautioned that CED could potentially lead to significant burdens on providers and patients, significantly limiting access. The discussions explored potential paths forward for stakeholders to address these issues effectively.

## Session I: Current mAb Landscape

This session provided an overview of current mAb therapeutics in the development pipeline and the foundational challenges and opportunities that these drugs present to patients, clinicians, manufacturers, and payers. Participants considered the links between amyloid reduction and measurable, meaningful clinical improvements in patients' cognition. Discussion also addressed how these drugs could be appropriately paid for and allocated, especially as further evidence from clinical trials and real-world studies is generated.

Discussants outlined the current anticipated timelines and evidence development for mAbs in the pipeline, and noted the importance of focusing on the entire drug class of mAbs for AD.

### *Current Pipeline*

The discussion addressed the evidence base of AD mAb therapeutics currently being assessed in clinical trials. Multiple agents are moving towards marketing applications to FDA and, consequently, are likely to provide more insights about the validity of amyloid plaque reduction as a surrogate marker and the potential of this class to be an effective new therapeutic option for early AD patients. However, the products in development have distinct development programs, enrolling patients with somewhat varied characteristics and using similar but distinct methods of assessment. This led to some discussion of how to advance knowledge about AD mAbs beyond recent FDA regulatory actions.

Industry representatives discussed publicly-available information on the current status of mAb therapeutics in ongoing clinical trials as well as the approaches taken to determine safety, effectiveness, and approaches to use (e.g., long-term treatment, fixed duration, treatment based on plaque reduction, etc.). The mAb treatments that are nearest to potential submission for FDA approval aim to reduce amyloid plaque for early-stage dementia patients. Discussants noted the pressing need to associate these changes in biomarkers with clinical study endpoints that assess the cognition and functional abilities of patients. Multiple manufacturers are aiming to have more concrete evidence about how these drugs impact clinical endpoints within the next year. Some discussants addressed the safety concerns with therapeutics of this type, as clinical trials have reported amyloid-related imaging abnormalities (ARIA)-E as a side effect in many patients, while others, including some clinical experts, noted that ARIA-E was also observed in patients who received the placebo, and that relatively few patients were symptomatic or faced significant lasting harm from ARIA-E.

### *Ongoing Needs*

Discussants commented on the significant need for more evidence on real-world effectiveness and impact on clinical outcomes of disease-modifying mAbs for AD, with some noting that the meaningful reduction in cognitive decline is not yet established by clinical trial data. With this in mind, one participant suggested that an objective starting price be set by a third party based on evidence review, with the goal of increasing access for appropriate patients and mitigating concerns from payers and providers about incorporating these new drugs into AD care, while research on AD biomarkers is still ongoing, asserting that the role of amyloid in AD was uncertain. As the evidence on links between biomarkers and patient outcomes improves, the price analysis could feasibly be updated.

A number of discussants disagreed with this assessment of the science. A participant noted that biomarkers for AD in cerebrospinal fluid (CSF) have been studied for approximately 20 years, and although amyloid's causal role in AD is not fully understood, the presence of amyloid acts as a catalyst for neural changes that are strongly related to neurodegeneration and changes in cognition. Another attendee added that unlike previous treatments, the new mAb treatments are showing concordance across trials, with stronger dose-dependent impacts on plaques and on measures of cognitive declines.

Contributing to the difficulty in assessing impacts on cognitive outcomes is the use of different evaluation metrics across trials, which also differs from other fields like oncology that have more experience with standardized measures and assessment tools used across trials. Participants agreed that with some promising trial results for this critical unmet medical need, there is a corresponding need for standardization of evaluative measures of meaningful outcomes (i.e., cognitive testing batteries,

assessment of daily living, and functional evaluations that are feasible to track in routine practice) and further studies using these measures to improve the evidence on treatment effects and value to patients and caregivers. Standardizing these measures could help address a range of evidence needs, including how current and planned clinical trials can contribute to evidence on the class as well as evidence on individual products, and how to develop efficient, non-burdensome systems to accrue relevant data for real-world evidence (RWE) to add to the evidence on the effect of covered mAbs on AD patients' quality of life and disease progression.

Participants also discussed the need for more evidence on subgroups of patients and those that may have particular safety considerations. They emphasized the importance of ensuring that emerging mAb treatments for AD are prescribed to the patient population that will receive the most benefit; the evidence in clinical trials to date involves relatively early-stage patients.

## Session II: Opportunities for Gathering Clinical Evidence for Promising AD mAb Treatments

This session explored the potential approaches to generating the further clinical evidence that would be helpful to payers in determining the coverage and pricing of mAb treatments for AD. The session included comments about the heterogeneity of AD and the multiple factors influencing AD progression across patients, which provided context around the difficulties payers are facing in determining how to cover these drugs for different patients, especially with a substantial market price. This led to further discussion around the value and feasibility of further randomized controlled trials (RCTs) to assess mAb effects, and how to develop useful RWE and ensure equitable access to treatments. Attendees emphasized the important role of CMS in setting a precedent for coverage and payment determinations.

### *Data & Standardization Needs*

Participants widely agreed that, along with ongoing and planned clinical trials, more RWD should be collected on utilization and outcomes associated with these drugs – as noted above, preferably using standard measures to help address key questions about the class. Because access to mAb treatments relies upon a specific diagnosis, and patients respond differently, diagnostic criteria need to be clear – yet trials and real-world studies should encourage further refinement in diagnostic tools [e.g., alternatives such as blood tests to positron emission tomography (PET) and CSF biomarkers for diagnosis], and studies that provided more evidence on the impact of patient factors like comorbid conditions or genomic profiles that may influence response and side effects.

Some commenters noted that, given the magnitude of the health and cost issues involved, additional efforts are needed across stakeholders to leverage existing data and conduct further studies to better assess the value of new AD treatments. One attendee noted that clinical expert groups are working to publish appropriate use recommendations for prescribing mAbs for AD and managing side effects in the near future, in hopes of guiding care decisions based on the current evidence.

One participant highlighted that registries and other study infrastructures are already in place (e.g., at NIH, PCORI, etc.) that are collecting data on AD diagnosis, disease progression, and biomarkers for some populations or could be retasked to do so. Additionally, CMS is implementing the iMPACT Act, which

requires standardized data collection to support quality measurement and improvement in the postacute care setting, which would include many beneficiaries with AD or cognitive impairment. The CMS Data Element Library thus offers another piece of the starting foundation for standard data collection that could be valuable to stakeholders in developing further evidence related to AD treatments.

### *Other Considerations*

Stakeholders also discussed equity concerns with mAbs that are highly priced and that require specialized care teams, costly imaging for diagnosis and monitoring, and effective management of any complications. If payers limit access to treatment, or impose high copayments, access is likely to be inequitable for those with more limited engagement with the health care system and with less access to relevant specialists (e.g., rural patients) or those who do not have supplemental insurance for the substantial copays (copays for outpatient drugs and imaging are 20 percent in Medicare Part B). These inequities might be exacerbated if payers decide not to cover at all. Some participants noted that equity concerns would be lessened if the out-of-pocket price to patients was substantially lower; others noted that patients might prefer additional financial support that could also be used for other AD-related interventions besides drugs.

Stakeholders discussed how to improve equitable access to an entire care model that would support appropriate use of new mAb treatments: steps for diagnosis and eligibility determination, including diagnostic testing and specialist visits; shared decisionmaking for a patient to make an informed decision based on the evidence relevant to their own circumstances and preferences; ongoing monitoring and appropriate treatment for side effects or adverse reactions to treatment; and appropriate decisionmaking and counseling about when treatment should be stopped.

Participants noted practical and ethical issues with continuing RCTs for data generation once a treatment had been approved, which would likely require some share of participants to receive a placebo treatment. Participants considered some ideas related to conducting feasible and worthwhile RCTs using alternatives to use of placebo controls, such as comparing mAb use to a set of evidence-based, non-pharmaceutical interventions such as exercise and cognitive stimulation programs and supports to reduce social isolation, or (if multiple drugs become available) comparative effectiveness studies. Participants also considered observational approaches using RWD to help inform appropriate use, coverage, and payment, such as registry studies of AD progression across different types of beneficiaries, alternative clinical care models including telehealth support and remote patient monitoring, and data collection related to predicting and managing side effects.

Some attendees noted that coverage and pricing would likely evolve between initial approvals and further evidence development on specific drugs and on the class, and that coverage with postmarket evidence development could encourage this evolution if implemented effectively.

Participants expressed some support for manufacturers and payers working together to ensure timely and equitable access to treatments in the class, including developing more consensus on how to assess the value of AD treatments and how to improve the evidence on value. Participants also discussed potentially using alternative models for payment such as tying some payments to outcomes or study results or using more population-based payments (per-member per-month) that are more predictable.

Stakeholders interacting with AD therapeutics from all angles expressed the importance of developing these ideas further, for both better evidence and better care models to support coverage, payment, and access for these new therapies.

### Session III: Looking Forward

The final session of the meeting discussed potential further opportunities to address stakeholder concerns about mAbs for AD and foster cross-cutting collaborations to achieve these goals. Participants emphasized the need for payers to collaborate with patients and clinicians to give patients the best care possible through efficient protocol- and data-driven decisions. The discussion also addressed the differences between the FDA's standard of "safe and effective" and CMS' standard of "reasonable and necessary" that is the basis of each agency's approach to data and evidence review.

#### *Effective Coverage*

Participants discussed the difficulties that come with making coverage decisions on high-demand drugs post-approval, especially ahead of the completion of an ongoing CMS NCA and ultimate NCD. The NCA that CMS conducts before issuing the AD NCD is expected to be a nine-month process. Payers are also putting needed administrative processes in place, including for the collection of new product codes, and providers are learning about how to submit claims effectively for payment. During this initial period, treatment use is likely to be limited and uneven.

Conversation about CMS coverage sparked further discussion around the need for meaningful, standardized data collection related to key payer questions, to help expedite this process in the future. In areas where postmarket evidence is valuable, and data collection for needed studies is not so burdensome as to significantly reduce access (e.g., for certain participating sites that are able to contribute to registries or even randomized trials), CMS could utilize CED to address evidence gaps related to "reasonable and necessary" coverage determinations when additional mAb treatments come to market. CED could be tied to a set of feasible clinical studies, and input to CMS from stakeholders in the coming weeks would help to further elucidate how these studies could be designed and conducted. Further, attendees noted that CED could present opportunities for new partnerships with clinical and data organizations, ultimately accelerating other ongoing research in the AD mAb space.

#### *Future Directions*

While payers described a range of areas where they desired additional evidence on the impact of mAb AD treatments, stakeholders agreed that more effective collaboration could advance innovation in the Alzheimer's space. As one attendee noted, any opportunity for slowing disease progression is important to AD patients and their caregivers, and that good evidence on the expected benefits and risks of treatment is crucial for realizing that opportunity. It was also noted that these drugs and future drug combinations may get better, as has happened in many other areas of medical progress. With investment in such treatments expanding, and with the potential for nonpharmaceutical interventions to help improve functional outcomes and quality of life for AD patients, stakeholders should work together on approaches to help assure that effective studies can be conducted to bring products to market and develop actionable postmarket evidence. Much is at stake for AD patients and their caregivers.