**Prospective Study on Anti-Amyloid-β Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Coverage of Evidence Development (The Anti-Aβ mAb CED Study)**

Brief Summary:
This protocol outlines the methods for a Centers for Medicare and Medicaid Services (CMS) Prospective Study on Anti-Amyloid-β Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Coverage of Evidence Development (The Anti-Aβ mAb CED Study). It is a prospective, longitudinal study using clinical data, patient assessments, and administrative claims data of the Medicare population.

Study Overview:

1. Clinicians will conduct a neurocognitive evaluation to determine patient eligibility by confirming a clinical diagnosis of MCI due to AD or mild AD dementia, and the presence of amyloid using biomarker testing including imaging (amyloid PET), cerebral spinal fluid (CSF) studies, and/or blood tests.
2. For all Medicare beneficiaries receiving anti-Aβ mAb treatment for MCI due to AD or mild AD dementia the prescribing clinician will assess the patient's baseline clinical status by cognition and function assessments using validated tools appropriate for use in the MCI with AD and mild AD dementia populations and submitting these data to CMS via the dedicated CMS CED submission portal every six months for up to 24 months (five total assessments).
3. In addition to performing the required cognition and function assessments, prescribing clinicians will need to report on the patient's use of anti-platelet and/or anti-coagulation therapy and whether the patient has developed new amyloid related imaging abnormalities (ARIA) since the last assessment data submission. These evaluations will be further described below.
4. The primary outcome study completion date will be determined by achievement of the *a priori* minimum sample size for the primary outcome at the 24-month assessment.
5. The study results will be publicly posted on ClinicalTrials.gov within 12 months of the primary outcome study completion date.

**Detailed Description**:
On April 7, 2022 CMS issued an NCD that covers FDA approved monoclonal antibodies directed against amyloid for the treatment of AD under Coverage with Evidence Development (CED), when furnished in accordance with the coverage criteria specified in the NCD for patients who have a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia. The complete NCD decision memorandum is available on our website (see link below).
https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=305.

Study Design

| | |
|---|---|
| Study Type: | Observational |
| Estimated Enrollment | See sample size estimation below |
| Observational Model: | Cohort |

| | |
|---|---|
| Time Perspective: | Prospective, longitudinal |
| Official Title: | Prospective Study on Anti-Amyloid-β Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Coverage of Evidence Development (The Anti-Aβ mAb CED Study) |
| Actual Study Start Date: | July 06, 2023 |
| Estimated Study Completion Date: | June 2028 |
| Primary Objective #1: | Primary Objective #1 is to assess whether anti-Aβ mAbs meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice. |
| Primary Outcome #1: | Primary Outcome #1 will focus on determining whether there has been statistically significant stability in daily living functional activities over 24 months. |
| Outcome measure: | Function and cognition will be primarily measured using the Functional Activities Questionnaire (FAQ) and the Montreal Cognitive Assessment (MoCA©). |
| Primary Objective #2: | Primary Objective #2 is to investigate whether benefits, including the primary outcome defined above, and harms such as brain hemorrhage and edema, associated with use of the anti-Aβ mAb vary according to characteristics of patients, providers, and clinical setting. |
| Primary Outcome #2: | Benefits will be defined as the primary outcome noted above; harms will be defined primarily as the occurrence of ARIA-E and ARIA-H (also described above). Additional benefits and harms, listed as secondary endpoints, will be included as data and feasibility allow. |
| Primary Objective #3: | Primary Objective #3 is to investigate how clinical benefits and harms change over time. |
| Primary Outcome #3: | Occurrence and frequency of ARIA-E and ARIA-H defined above will also be evaluated at 6 months, 12 months, 18 months, and 24 months, respectively. As feasible, additional secondary endpoints and/or subgroup analyses will be examined at additional timepoints. |
| Inclusion Criteria: | All Medicare beneficiaries with a clinical diagnosis of MCI due to AD or mild AD dementia, both with confirmed presence of Aβ pathology consistent with AD, and receiving monoclonal antibodies directed against Aβ as part of this CED. |
| Exclusion Criteria: | There are no exclusion criteria for this CED study. |

Sample Size Estimation

| Assumed Percentage of Subjects Experiencing an Increase of ≥ 3 Points on FAQ | Target Confidence Interval Width | Sample Size for Each Clinical Subgroup (MCI Due to AD, or Mild AD Dementia) | Total Sample Size |
|---|---|---|---|
| 30% | 3% | 3650 | 7300 |
| 40% | 3% | 4170 | 8340 |
| 50% | 3% | 4340 | 8680 |
| 60% | 3% | 4170 | 8340 |
| 70% | 3% | 3650 | 7300 |

*Figure 1. Anti-Aβ mAb CED Study Protocol Overview*

## The Anti-Aβ mAb CED* Study Overview

| | Enrollment | 6 Months F/up | 12 Months F/up | 18 Months F/up | 24 Months F/up | Study Analysis |
|---|---|---|---|---|---|---|
| **Study Population** | | | | | | |
| **Inclusion Criteria:** All Medicare patients with a clinical diagnosis of mild cognitive impairment due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD | X | X | X | X | X | |
| **Anti-Aβ mAb Treatment** | Anti-Aβ monoclonal treatment administered per FDA label and clinical practice guidelines | | | | | |
| **Data Collection**** | Clinical diagnosis & testing results | Clinical diagnosis & testing results | Clinical diagnosis & testing results | Clinical diagnosis & testing results | Clinical diagnosis & testing results | |
| | **Cognition:** -MoCA© or -Other cognition instrument<br>**Function:** -FAQ or -Other function assessment | **Cognition:** -MoCA© or -Other cognition instrument<br>**Function:** -FAQ or -Other function assessment | **Cognition:** -MoCA© or -Other cognition instrument<br>**Function:** -FAQ or -Other function assessment | **Cognition:** -MoCA© or -Other cognition instrument<br>**Function:** -FAQ or -Other function assessment | **Cognition:** -MoCA© or -Other cognition instrument<br>**Function:** -FAQ or -Other function assessment | |
| **Outcomes Assessment & Analyses** | | Cognition & Function | Cognition & Function | Cognition & Function | Cognition & Function | **Study Outcomes:**<br>1. Slow in Decline of Cognition and Function<br>2. Incidence of Brain Hemorrhage and Edema & Subgroup Analyses<br>3. Benefits & Harms Over Time |
| | | Benefits & Harms | Benefits & Harms | Benefits & Harms | Benefits & Harms | |
| | | | Benefits & Harms Over Time | Benefits & Harms Over Time | Benefits & Harms Over Time | |
| **Study Reporting** | | | | | | Annual reports: TBD by CMS<br>Final Report and Public Posting within 12 months following study completion |

*Prospective Study on Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Coverage with Evidence Development (The Anti-Aβ mAb CED Study), Anti-Aβ=Anti-Amyloid Beta, AD=Alzheimer's Disease, mAb=monoclonal antibodies, CED=Coverage with Evidence Development
**Data Portal Collection Form and definitions (Appendix A)
FAQ=Functional Activities Questionnaire, MoCA©=Montreal Cognitive Assessment, TBD=To Be Determined