Georgia Memory Net Proposal for Anti-Amyloid Monoclonal Antibody Coverage with Evidence Development

Alzheimer's disease is a devasting neurodegenerative illness impacting millions of Americans including patients and caregivers. Treatments have been limited to symptomatic therapies leading to the pervasive sentiment that 'nothing can be done'; however, recent advances in the field have created excitement and hope for patients, families, and healthcare providers. On 6 January 2023, the anti-amyloid monoclonal antibody (mAb) lecanemab received accelerated approval from the Food and Drug Administration (FDA). In addition to evidence for amyloid clearance, results of a large phase 3 trial (Clarity AD) showing clinical benefit meeting all primary and secondary outcomes at 18 months was reported in December 2022[1]. An earlier phase 2B trial of lecanemab failed to meet primary outcome on the Alzheimer's Disease Composite Score (ADCOMS) at 12 months, but showed significant benefit on ADCOMS, Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14) at 18 months[2]. Based on these results, the FDA advisory committee recommended full approval on 9 June 2023 and a final FDA decision is anticipated by 6 July 2023. A similar medication, donanemab, also recently demonstrated positive results in a large trial. Despite the positive trials, questions remain about anti-amyloid mAbs efficacy as well as how they will perform in a real-world setting. The Centers for Medicare & Medicaid Services (CMS) released a National Coverage Analysis (NCA) Memo (CAG-00460N) with a framework for deploying anti-amyloid mAbs in a way that improves understanding of benefit and harm. We therefore propose to capitalize on the expertise of our team at Emory University and the NIA funded Goizueta Alzheimer's Disease Research Center (ADRC), in collaboration with the Georgia Memory Net (GMN), to address the coverage with evidence development (CED) criteria outlined in the NCA with 3 Aims.

Aim 1. Demonstrate that FDA approved anti-amyloid mAbs meaningfully improve health outcomes for patients in broad community practice. The GMN infrastructure will be used to deploy a prospective comparative study (registry) to track metrics that demonstrate meaningfully improved outcomes from a broad range of academic (Emory), academic affiliated (GMN Memory assessment clinics [MACs]), and other community practices. FDA label instructions and best practices inclusion/exclusion criteria will be used to select patients with mild cognitive impairment (MCI) due to AD or mild AD dementia for anti-amyloid mAb treatment. This will occur in the state of Georgia, which is representative of the national population.

Aim 2. Understand how patient characteristics, treating clinicians, and clinical settings impact benefits and harms (brain hemorrhage and edema) of FDA approved anti-amyloid mAbs. We will use the rich dataset collected in the GMN patient registry to define patient, clinician, and clinical setting characteristics that maximize patient benefit and minimize harm from side effects. Coupling anti-amyloid mAb therapy to the GMN diagnostic and care model will also confer additional insights on scalability, interplay with community services resources, nonpharmacological interventions, and collaborations with local primary care physicians.

Aim 3. Define how benefits and harms of FDA approved anti-amyloid mAbs change over time. The limited time frame of anti-amyloid clinical trials has made it difficult to define the long-term impacts of treatment, including benefits and harms. The expected duration of therapy is also unclear, necessitating a careful balance between opportunity for continued benefit with risks and fiscal responsibility to the healthcare system. We will compare emerging novel insights from the field with metrics and trends from the GMN patient registry to help refine best practices in longitudinal treatment with anti-amyloid mAbs to optimize patient (and family) quality of life.

What is the Georgia Memory Net (GMN)?

This study will be conducted through GMN, an initiative that was launched in 2018 to build statewide capacity for early and specific diagnosis of Alzheimer's disease and related dementias (ADRD), improve patient and caregiver support, and provide access to emerging disease-modifying therapies[3]. The GMN supports Memory Assessment Clinics (MACs) geographically distributed at 7 sites around the state (**Figure 1**) with common data elements modeled on best practices developed in the Emory University Cognitive Neurology Memory Assessment Clinic over the past 25 years. Subspecialty-certified Cognitive and Behavioral Neurologists (United Council for Neurological Subspecialties) and expert Neuropsychologists based at Emory provide training to Neurologists, Primary Care Physicians, Geriatricians, and Advanced Practice Providers to guide and support development of diagnostic and management expertise that is generally not available outside of tertiary referral centers. Psychometric technicians are trained to administer a standardized battery of cognitive testing in diagnostic assessments across all sites. Support for patients and caregivers is an integral element of the care model, and Community Services Educators (CSEs) are embedded within each GMN MAC. CSE training and oversight is provided by social workers and other experts on caregiving based at Emory. Active outreach and education of primary care providers is a third pillar of the GMN with the goal of promoting earlier recognition of cognitive decline and referral of patients with ADRD to optimize care and maximize utility of disease-modifying therapies which are only effective at early stages of disease. Lastly, the activities of the GMN are underpinned by a robust IT infrastructure (**Appendix 1**), the GMN Portal, which integrates with multiple health systems through an HL7 interface and supports shared data elements in the assessment of GMN patients. The GMN infrastructure and care model provides an optimal real-world testing ground for evidence development on the effectiveness, safety, and appropriate use of anti-amyloid mAbs in the Medicare population.

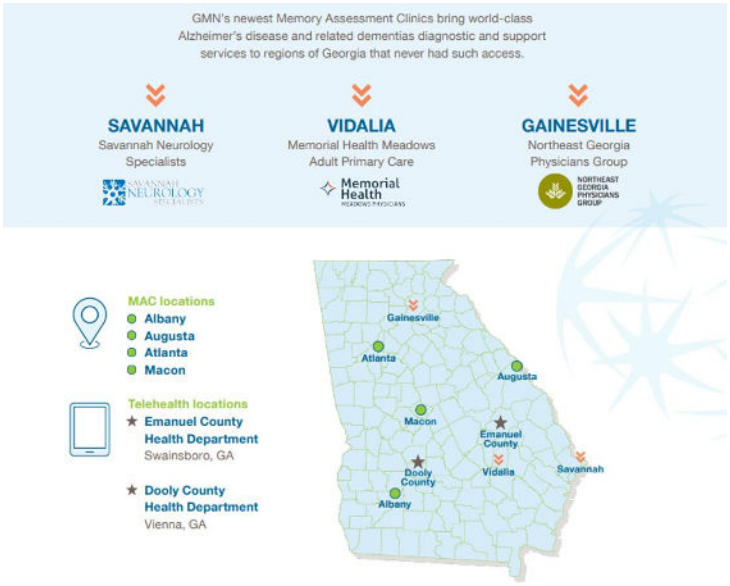

Figure 1: GMN Sites. Four existing Memory Assessment Clinics in Albany, Augusta, Atlanta, and Macon are being expanded with addition of three new selected sites in Gainesville, Savannah, and Vidalia to improve geographical coverage. Exploratory Telehealth locations are being developed in collaboration with the Georgia Department of Public Health which maintains offices and at least one public health nurse in each of Georgia's 159 counties.

Study Design

Aim 1: Demonstrate that FDA approved anti-amyloid mAbs meaningfully improve health outcomes for patients in broad community practice.

A. Study sites:
The Emory Clinic and GMN MACs will serve as primary sites for the comparative study registry. This is to ensure that clinical expertise in neurocognitive evaluation and infrastructure to provide treatments is consistent with all aspects of the FDA labeling, including diagnosis and safety monitoring. Similarly, the Emory Clinic and GMN MACs have multidisciplinary teams and best practices to ensure optimal medical management and tracking of patient outcomes, regardless of eligibility for or treatment with anti-amyloid mAbs (see above). Additional services including the Emory Cognitive Empowerment Program, caregiver support programs, and educational resources in development will further augment best practices. Adjunct sites will also be encouraged to participate in this comparative study registry to ensure data capture across broad community practice. All participating sites must demonstrate readiness for comprehensive patient care, safety monitoring, and registry participation.

B. GMN anti-amyloid mAbs registry:
GMN Portal (**Appendix 1**) will serve as the registry. Although the GMN Portal has robust capabilities for medical record integration and capturing patient data (demographics, neuropsychological testing, care needs assessments, care plans, visit time points), modifications will be implemented to accommodate additional data capture elements including specific safety information related to amyloid-related imaging abnormalities (ARIA), results of amyloid positron emission tomography (PET) scans, and to facilitate access for adjunct sites that are not a part of the GMN.

C. Patient population:
The patient population served by the Emory Clinic, GMN MACs, and other practices across Georgia are representative of Georgia and reflects the national population of patients with MCI due to AD or mild AD dementia. Georgia has a wide range of demographics including urban and rural populations. Specific efforts have been made to facilitate access to underserved populations based on race, geography, and socioeconomic status (SES). The GMN MAC at Grady Memorial Hospital system serves a largely minority and low SES population, and sites in Vidalia and Albany serve a largely rural population.

D. Patient selection for study enrollment:
Guidelines for patient selection for possible treatment with anti-amyloid mAbs have been developed for lecanemab based on FDA-labeling and provider expertise (**Appendix 2**). Guidelines for other FDA-approved mAbs will be developed in similar fashion. These guidelines will be disseminated across all sites participating in the GMN anti-amyloid mAbs registry. Most inclusion and exclusion criteria were adapted from the phase 3 Clarity AD trial. Inclusion criteria are designed to avoid denying individuals with early-stage AD who may fail to meet rigid testing thresholds. This may impact patients with an atypical clinical presentation such as primary language impairment or posterior cortical atrophy that may depress performance on cognitive testing. Race, ethnicity, and educational attainment are also well-established factors that may lower scores on standard measures such as the MMSE or MoCA[10-12], and strict adherence to cutoff scores would produce inequities in access to an effective treatment. A major limitation of existing evidence for benefits and harms associated with amyloid mAbs is the lack of broad representation reflective of the Medicare beneficiary populations. Available historical data from biomarker-confirmed patients with MCI or mild dementia due to AD who have been followed in the Emory Cognitive Neurology Clinic will serve as a comparator group. In addition, patients seen at Emory and across GMN MACs who are eligible for amyloid mAbs but not interested in receiving treatment and those who meet cognitive and functional criteria but are ineligible due to other reasons will serve as a prospective comparator group to address potential impact of different clinical settings.

E. Standard instrument collection:
Evaluation of patients seen in the Emory and GMN MACs includes standard instruments for cognitive and functional abilities. Processes for data collection in participating adjunct sites will need to be developed. These measures include the Montreal Cognitive Assessment (MoCA)[13], Quick Dementia Rating Scale (QDRS)[14,15], Rey Auditory Verbal Learning Test[16], Category Fluency Test, Letter Fluency Test, Trail-Making Test A & B, Digit Span, Multilingual Naming Test, and Rey-Osterreith Complex Figure Test[17]. PHQ8 and GAD7[18] are collected to monitor symptoms of depression and anxiety. Functional measures include the Functional Activities Questionnaire (FAQ)[19] and the Lawton and Brody Activities of Daily Living scale (ADL/IADL)[20]. Additional instruments include the Benjamin Rose Institute Caregiver

Strain Instrument (BRI-CSI), Care Needs Assessment Tool (CNAT), and the Zarit Burden Interview which are used to assess caregiver burden and needs. Quality of life measures including the PROMIS10 and/or Quality of Life in AD (QoL-AD) will also be captured.

F. Outcomes assessments:

Baseline, Q6 month, and annual assessments will be administered to participants in the registry (**Table 1**). All cognitive measures and questionnaires are provided and captured through a Research Electronic Data Capture (REDCap)[21] instance in the HIPAA-compliant GMN Portal on AWS. Dashboards will be used to review aggregate data and individual trajectories for patients on anti-amyloid mAbs and comparator groups.

Table 1: Monitoring Response to Anti-Amyloid mAbs

	Baseline	6-month	Annual
Full battery cognitive test and QDRS	X		X
MoCA and QDRS only		X	
FAQ, ADL/IADL, BRI-CS/CNAT/Zarit	X	X	X
GAD7, PHQ8	X	X	X
PROMIS10/QOL-AD	X	X	X

G. Safety monitoring:

This will be addressed below in **Aim 2** with **Appendix 3** for reference.

H. Public Data Release:

Per CMS CED guidelines, results from **Aims 1-3** will be made public no later than 12 months from the end of data collection through peer reviewed journals. Every effort will be made to quickly release any interim results/data that may impact the ongoing care of patients.

Aim 2. Understand how patient characteristics, treating clinicians, and clinical settings impact benefits and harms (brain hemorrhage and edema) of FDA approved anti-amyloid mAbs.

A. Impact of patient characteristics, treating clinicians, and clinical settings on benefits of anti-amyloid mAbs:

The GMN anti-amyloid mAbs registry will capture relevant patient demographics, medical problems, and medications as well as details on the treating clinician (specialty) and clinical setting (academic, affiliated GMN, adjunct site). This information will be correlated to outcomes measures from Aim 1 for patients on anti-amyloid mAbs and comparator groups to identify features that impact benefit. Importantly, juxtaposing mAb treatment with wrap-around care, including nonpharmacological interventions (lifestyle modifications, care plans, social work, community services referrals) via multidisciplinary teams and best practices in the Emory and GMN MACs will provide additional insights about optimizing patient care.

B. Impact of patient characteristics, treating clinicians, and clinical settings on harms of anti-amyloid mAbs:

The primary safety concern with the use of anti-amyloid mAbs relates to the development of ARIA including occurrence with edema (ARIA-E) and hemorrhage (ARIA-H). For lecanemab, safety MRI scans (**Appendix 3**) will be scheduled following the protocol used in the phase 3 Clarity AD trial and prescribing information released by the FDA in January 2023. Additional safety MRIs will be needed to monitor ARIA if it should develop, especially if symptomatic. Given the increased risk for ARIA, *APOE* ε4 homozygous individuals who decide to pursue treatment will be monitored with an additional early safety scan prior to their 3rd dose. The MRI schedule for other anti-amyloid mAbs will follow FDA guidance. Orders for safety MRI scans will be incorporated into the order set initiating treatment with the anti-amyloid mAb and scheduled in advance. MRI orders will also specify reasons for scans (monitoring for ARIA) to alert Neuroradiology. In addition to regular Neuroradiology review and report, the ordering provider will also review the MRI to confirm absence of ARIA. For GMN and adjunct sites which do not have local expertise in Neuroradiology or Nuclear Medicine, formal review will be obtained through Emory Radiology through external consultation. Tracking data for ARIA will be captured in GMN portal and may also be captured in the health system's EHR via integrated tools such as Epic Patient Registry or Workbench. As with Aim 2A above, ARIA frequency and correlated patient characteristics, provider information, and clinical settings will be used to identify elements that increase or decrease the risk for harm.

Aim 3. Define how benefits and harms of FDA approved anti-amyloid mAbs change over time.

Published data have established the efficacy of lecanemab for clearance of amyloid and slowing of decline in early-stage AD up to 18 months. However, it is unknown whether there is benefit for continuing lecanemab dosing for longer periods and following amyloid clearance. Similar data are also lacking for other anti-amyloid mAbs. In addition, individuals may experience clearance of amyloid at different rates. Evidence for rates of re-

accumulation of amyloid are limited, but analysis of results from individuals enrolled in the delayed open-label extension of the phase 2B lecanemab trial offer some guidance[22]. These results suggest that re-accumulation of fibrillary amyloid deposits detected by amyloid PET scans occurs with a half-life of about 4 years. However, recidivism rate of plasma Aβ42/40 ratio and pTau181 levels is more rapid with a half-life of 1.9 and 1.5 years, respectively. As it is believed that these plasma measures reflect changes in CSF, one might reasonably conjecture that declining levels of Aβ42/40 and increasing levels of pTau181 may serve as early indicators resurgent AD pathology. Additional evidence to guide long-term lecanemab dosing will require collection of longitudinal biofluid and imaging biomarkers.

A. Initial treatment regimen for anti-amyloid mAbs:

For lecanemab, infusions will occur every 2-weeks as indicated in the FDA labeling. Labeling is not yet available for other anti-amyloid mAbs but would be followed accordingly (ex: donanemab is likely to be a monthly infusion). After 18 months of lecanemab treatment, an amyloid PET scan with FDA-approved radiotracer will be performed to confirm clearance of amyloid pathology. Interpretation of amyloid PET scans by visual read and semi-quantitative standardized uptake value ratio (SUVR≤1.1) have shown good accuracy and agreement[23-25], and the choice of methodology may vary by site. It is anticipated that most individuals treated with lecanemab for 18 months will no longer have positive amyloid PET scans, and initial data on donanemab suggests this time frame may be shorter with that drug and duration of treatment with other mAbs will be guided by emerging data and FDA labeling. In those instances where persistent amyloid pathology is seen, every 2-week treatment with lecanemab will be continued for an additional 6 months with repeat amyloid PET scan until amyloid clearance is achieved. If an individual has progressed to moderate or severe stages of AD dementia during the initial 18 months of treatment and amyloid PET shows failure to clear amyloid pathology, treatment will be terminated.

B. Maintenance phase of anti-amyloid mAb:

Once amyloid clearance has been achieved, the need for continued treatment with anti-amyloid mAbs is unclear. Modeling of data from phase 2B lecanemab open label extension study participants who were off drug for an average of 2 years, suggests that the half-life for fibrillar amyloid re-accumulation is ~4 years. Other biomarker changes revert on a quicker time scale (~1.5-2.0 years). Given the known re-accumulation of amyloid pathology, maintenance therapy may be required to sustain clinical gains. Dosing frequency after 18 months (or after amyloid clearance) remains unclear and will need to be determined with additional evidence development. Plasma AD biomarker tests may prove to be more sensitive indicators, but none have been approved by FDA as *in vitro* diagnostic tests (IDT). Although it will not be required under the GMN registry protocol, collection of plasma samples under an IRB-approved protocol will be planned at Emory and encouraged at other GMN sites to facilitate evidence development for the appropriate clinical use of plasma biomarkers.

Until there is additional data to guide maintenance dosing with anti-amyloid mAbs, we propose two alternative approaches for individual patients based on the provider's judgment and in consultation with patients and families. In both instances, patient data will continue to be collected to advance evidence development in this important area. Option 1 will be to continue infusions based on label for the specific mAb until additional data are available to direct appropriate maintenance dosing. Option 2 (**Fig. 2**) will be to discontinue dosing after amyloid is cleared. Amyloid PET scans will be done every 6 months to monitor amyloid plaque recrudescence. In the case of lecanemab, a positive amyloid PET scan will prompt re-initiation of bi-weekly dosing with repeat PET scans every 3 months until scan confirms amyloid re-clearance.

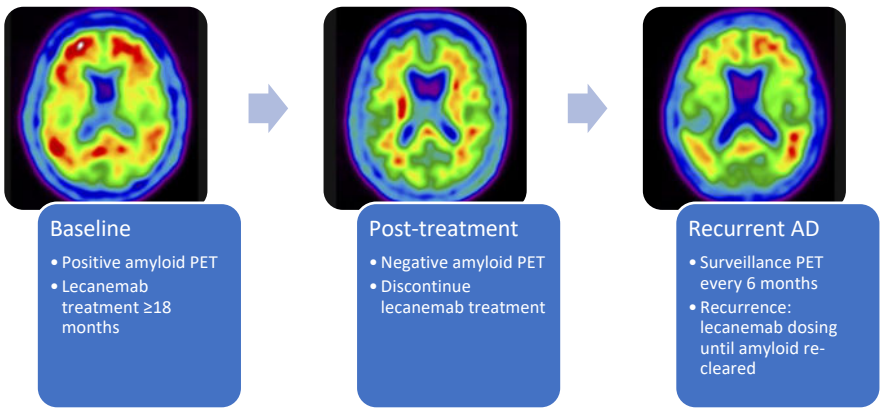

Figure 2. Schematic for initial maintenance dosing of lecanemab

C. Anti-amyloid mAb discontinuation:

The rationale for continuing disease-modifying therapy (DMT) such as that offered by anti-amyloid mAbs is to avoid later stages of severe dementia with attendant deterioration in quality of life as well as

increased financial burden driven by institutionalization. Any patient that has progressed to needing institutionalization should no longer receive any DMT, and placement into a Memory Care or Skilled Nursing facility will be specified as an endpoint for eligibility in the GMN registry and mAb will be discontinued. Individuals who have progressed beyond the MCI or mild dementia stages of AD may be continued in the GMN registry with PET surveillance, maintenance therapy, and data collection as appropriate for individual patients based on the judgment of their provider in consultation with their caregivers. Data driven guidance for discontinuation will emerge through examination of evidence developed under this CED.

D. Provisions for brain donation among treated patients:

Every effort will be made to encourage enrollment of patients on anti-amyloid mAbs in a brain autopsy program. We will use the Emory Goizueta ADRC autopsy-only enrollment option or other capture mechanism that may be created in the interim. The timing of this discussion would be left up to the provider; however, discussion as early as possible during treatment would be encouraged to avoid challenges with consent after cognitive decline and to ensure that any fatalities are well characterized to determine possible association with anti-amyloid mAb treatment. Standardized materials about autopsy will be developed and available for providers to help facilitate these autopsy discussions.

Appendices:
Appendix 1: GMN Technology Infrastructure

There are three primary applications that comprise the Georgia Memory Net portfolio:

- GMN Portal
- REDCap
- Rhapsody Integration Engine

These applications are integrated on the back end by Emory University's enterprise instance of Amazon Web Services.

These applications are illustrated in Figure 3:

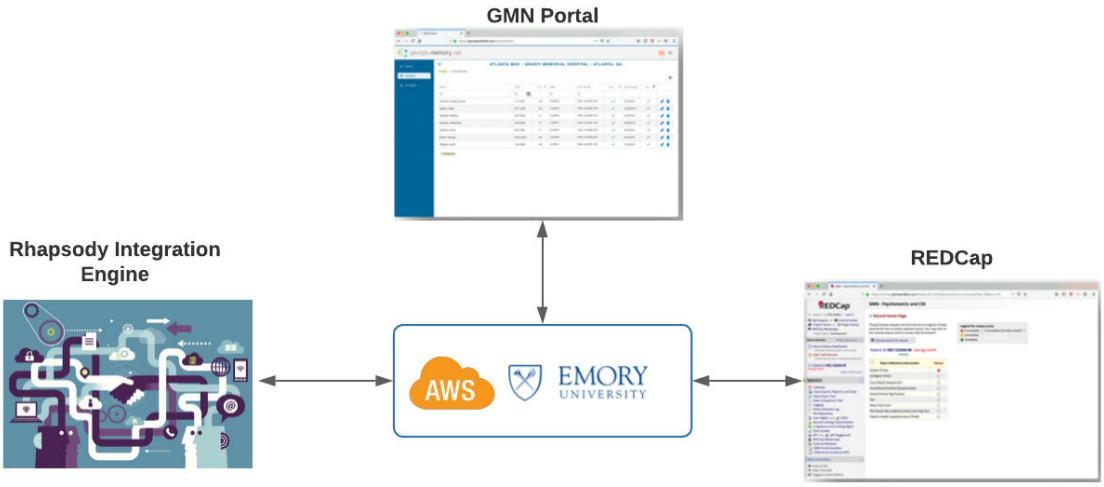

Figure 3 – Georgia Memory Net Applications

GMN Portal
GMN Portal is the central application for managing patients in the Georgia Memory Net program. Patients will be added in GMN Portal (manual entry or HL7) which will then enable assessments in REDCap.

GMN Portal will also provide post-assessment reports:

- Summary of Neurocognitive Screening
- Care Needs Summary
- Patient and Care Partner Care Plans

REDCap
REDCap is a purpose-built web application for building and managing surveys and databases. It is optimally designed for research-based data collection: "REDCap" is an acronym for "Research Electronic Data CAPture".

For GMN, Cognitive and Community Services assessments have been implemented in REDCap. Psychometricians and CSEs use REDCap to capture data from patients and their care partners. Generally speaking, REDCap is not a patient-facing application.

Rhapsody Interface Engine
A Rhapsody integration engine is embedded withing the GMN technology infrastructure to support the programs current and future data integration requirements. Current integration consists of the following:

- Inbound ADT and Scheduling HL7 2.x interfaces from MAC EHRs
- Outbound ADRD registry reporting to GA Department of Public Health

Amazon Web Services / Emory University

The back-end infrastructure for GMN applications is implemented in Amazon Web Services (AWS). This is Emory University's enterprise instance of AWS. The AWS environment provides network infrastructure, application hosting, databases and security. The GMN infrastructure is isolated from Emory University/Emory Healthcare.

Table 1 provides a summary of GMN application components:

Table 1 - Summary of GMN Components

Application Component	Type	Description
GMN Portal	Web Application	• Central interface for managing patients • Neurocognitive Summary report • Care Needs Summary report • Care Plan Creation Tool
REDCap	Web Application	• Psychometric assessments • Community Services assessments
Rhapsody Integration Engine	Infrastructure	• Inbound/outbound HL7 2.x ADT & Scheduling interfaces • FHIR support
Amazon Web Services / Emory University	Infrastructure	• Managed instance of AWS • Application hosting • Databases • Network • Security

Appendix 2: Inclusion/Exclusion Criteria and Special Considerations for Caution for Lecanemab :

Inclusion Criteria:

1. Age 50-90, inclusive
2. Diagnosis: Mild Cognitive Impairment (MCI) or mild AD with positive CSF or amyloid PET
3. Objective measurement of baseline cognition and function within past 3 months:
    a. Cognitive: MMSE ≥ 22, MoCA ≥ 16[4-6]
    b. Function: Independence in basic ADLs
    c. Function: FAQ ≤ 6 may justify inclusion with lower cognitive score if felt to be impacted by prominent language impairment or other factors affecting score[7]
4. MRI brain within last year and no exclusionary criteria
5. CBC, CMP, B12, TSH, PT, PTT, and INR without clinically significant abnormality
6. Informant/care partner/family available to attend follow-up visits to provide information regarding patient's cognitive and functional abilities
7. Consents to MRI, PET, and testing per protocol, including *APOE* testing, plasma biomarker testing, and data/sample sharing

Exclusion Criteria:

1. Any contraindication to MRI
2. MRI exclusion criteria:
    a. Acute or sub-acute hemorrhage
    b. Prior macro hemorrhage (>1 cm), subarachnoid hemorrhage, or known aneurysm
    c. ≥4 microhemorrhages
    d. Superficial siderosis
    e. Any finding that might be a contributing cause of the subject's dementia that could pose a risk to the subject or prevent safety MRIs.
3. Seizure within the past 6 months or history of refractory epilepsy.
4. Unstable severe psychiatric illness in past 6 months
5. History of bleeding disorder, blood clotting, or clinically significant abnormal results on coagulation profile (platelet count <50K; INR >1.5)
6. Uncontrolled diabetes (HgbA1c >9%)
7. Uncontrolled hypertension
8. History of unstable angina, MI, advanced heart failure, or clinically significant conduction abnormalities within past year.
9. End stage renal disease
10. Receiving active treatment for cancer (e.g., chemotherapy, biologics, or radiation therapy) with exceptions for maintenance therapies for cancer in remission (e.g., anti-estrogen for breast cancer)
11. Systemic illness or serious infection (e.g., pneumonia, sepsis, COVID19) in past 30 days
12. Immunological disease requiring immunosuppression, immunoglobulins, monoclonal antibodies, or plasmapheresis
13. Exclude if breastfeeding or if female patients of childbearing potential unable to practice highly effective contraception.
14. History of severe allergic or anaphylactic reactions or hypersensitivity to inactive ingredients (arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80).

Special Caution:

1. Patients requiring chronic anticoagulation
    a. Details not available to fully assess risk (pre-existing MCH, anticoagulation, ARIA-H, macrohemorrhage)
    b. Not excluded in Clarity AD trial and reportedly were not associated with increased risk (webinar)
    c. Macrohemorrhage reportedly occurred in 5/140 (3.6%) in patients on both lecanemab and anticoagulant (https://www.science.org/content/article/hail-new-antibody-treatment-alzheimers-safety-benefit-questions-persist)
2. If possible, consider option for alternative to anticoagulation for atrial fibrillation (e.g., LAA closure/Watchman)
3. *APOE* ε4 homozygosity is associated with 30-40% risk of ARIA, including about 10% risk of symptomatic ARIA. *APOE* genotyping should be strongly considered and discussed in the context of

risk assessment. If treatment is pursued in an *APOE* ε4 homozygous individual an additional early safety MRI should be obtained prior to the 3rd dose of lecanemab.

4. Consider potential increased or unknown risk if recent participation in a clinical trial for AD (unless assigned to placebo).
5. Provide adequate disclosure of potential high risk of tPA for acute stroke or other indication for acute anticoagulation (e.g., MI, PE, etc.) during treatment with lecanemab[8,9]

Appendix 3: Guidance for MRI Brain Safety Monitoring for Lecanemab: Detecting ARIA-E and ARIA-H:

1. Baseline brain MRI obtained within one year with no exclusionary criteria
2. Surveillance MRI scans
    a. Schedule before 5th, 7th, and 14th infusions
    b. For *APOE* ε4/ε4 homozygous individuals, an additional MRI scan should be done before the 3rd infusion based on case reports of severe adverse events that occurred in the first few doses.
    c. Schedule every 6 months thereafter throughout treatment and additional scan one year after treatment completed.
3. Mild, asymptomatic ARIA-E or ARIA-H
    a. ARIA-E: FLAIR hyperintensity <5 cm maximal dimension confined to sulcus or cortex/subcortex white matter
    b. ARIA-H: ≤4 new MCH or 1 new focal superficial siderosis
    c. Lecanemab dosing may be continued
    d. Monthly MRI scans until resolution of ARIA-E or stabilization of ARIA-H (absence of new ARIA-H)
4. Moderate ARIA-E (>5cm hyperintensity) or ARIA-H (>4 new MCH, >1 superficial siderosis)
    a. Suspend lecanemab dosing
    b. Monthly MRI until resolution/stabilization of ARIA before resuming dosing
5. Any symptomatic ARIA
    a. Suspend lecanemab dosing
    b. Monthly MRI until resolution/stabilization of ARIA and symptoms resolved

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