University of California (UC) Anti-Amyloid Beta Antibody Infusion Protocol

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1. Inclusion and Exclusion Criteria for Consideration of Anti-Amyloid Antibody Treatment

1.1. Inclusion Criteria

1.1.1. Ages 50–90 years of age, inclusive (with additional consideration for physician judgment in patients under 50 or over 90 years of age);

1.1.2. Is actively co-managed by a primary provider with expertise in dementia care;

1.1.3. Based on a comprehensive clinical diagnostic evaluation by a dementia specialist, has a clinical syndrome believed to be consistent with underlying symptomatic Alzheimer's disease clinical phenotypes including the following[1]:
- 1.1.3.1. Mild cognitive impairment[2];
- 1.1.3.2. Probable Alzheimer's disease dementia [3,4];

1.1.4. Level of cognitive impairment consistent with mild cognitive impairment or mild dementia as defined by:
- 1.1.4.1. Retained functional independence or early mild loss of functional independence defined as:
  - 1.1.4.1.1. Retained ability to manage instrumental activities of daily living (IADLs, such as finances, medications, driving, etc.) or minor changes in only some IADLs with no changes in basic ADLs;
  - 1.1.4.1.2. Functional status consistent with a Clinical Dementia Rating (CDR)[5] Scale Global score of 0.5 or early transition to a score of 1 (though a formal CDR score need not be obtained for eligibility);
- 1.1.4.2. Cognitive impairment that is limited in severity (mild range except for memory impairment) and/or scope (limited to one or a few cognitive domains) as determined by cognitive testing within 3 months of screening. Cognitive screening cut-off scores may be helpful (an MMSE[6] ≥ 22 or an equivalent[7] MoCA[8] score ≥ 17) but their use is discouraged when affected by educational attainment, language of test administration, or primary deficits in language or vision;

1.1.5. Positive biomarker information consistent with Alzheimer's disease pathology as indicated by at least one of the following[1]:
- 1.1.5.1. Aβ PET scan (using an FDA-approved tracer) consistent with elevated amyloid;
- 1.1.5.2. CSF analysis at a CLIA-approved lab consistent with underlying AD pathology;

Note: Plasma biomarkers alone may not be used to establish eligibility, but may be used to "rule out" the presence of an eligible diagnosis. Patients with

borderline biomarker values may be reviewed by the local infusion core review board;

1.1.6. Recent brain MRI including FLAIR, DWI, and heme sequences (SWI preferred, but GRE and T2 star acceptable) within 12 months prior to expected time of treatment initiation;

1.1.7. Eligible and willing to receive requisite safety MRIs in screening during at least the first year of treatment (and beyond one year of follow-up if clinician judgment deems it necessary for patient safety);

1.1.8. INR/PT, aPTT, and complete blood count including platelet count within the normal range of the resulting CLIA-approved lab within 3 months prior to treatment;

1.1.9. Women of childbearing potential and all men must agree to adequate, highly effective, methods of contraception during drug treatment period;

1.1.10. Able to understand the risks of lecanemab (including relative risk associated with APOE alleles) and provide ongoing informed consent for treatment;

1.1.11. A care partner (who interacts with the patient regularly enough to follow for adverse events and clinical progression) is strongly recommended;

1.1.12. Prior genetic testing for APOE allele is required and appropriate education of associated ARIA risk is strongly advised as part of informed consent procedures. If a patient is an APOE-ε4 carrier, they must fully understand their increased risk of ARIA before proceeding, particularly if they are a homozygous carrier.

1.2. Exclusion Criteria

1.2.1. Cognitively unimpaired and asymptomatic individuals;

Subjective cognitive impairment without confirmation of deficits from a reliable collateral source of information AND confirmatory neurocognitive testing;

1.2.2. Moderate or late-stage dementia, involving loss of independence in multiple instrumental activities of daily living or at least one basic activity of daily living (i.e., CDR Global Score >1);

1.2.3. Significant findings on brain MRI including:
- 1.2.3.1 Acute or subacute hemorrhage or infarction;
- 1.2.3.2 More than 4 microhemorrhages (any location), defined as 10mm or less at greatest diameter;
- 1.2.3.3 One or more macro hemorrhages, defined as 10mm or larger at greatest diameter;

1.2.3.4 One or more regions of superficial siderosis;
1.2.3.5 One or more cortical infarctions;
1.2.3.6 Two or more lacunar infarctions;
1.2.3.7 Evidence of substantial white matter changes concerning for ischemic microvascular disease including:
1.2.3.7.1 Irregular periventricular white matter T2 hyperintensities extending into deep white matter and beginning confluence;
1.2.3.7.2 Or large confluent areas of deep white matter T2 hyperintensities;
1.2.3.8 Intraparenchymal lesion that is concerning for malignancy or likely to increase the risk of herniation in the event of ARIA-E or ICH;
1.2.3.9 Other evidence of active neuroinflammatory disease;

1.2.4 Treatment with anticoagulants (e.g., DOACs, warfarin, enoxaparin, heparin, fondaparinux);

1.2.5 Dual antiplatelet therapy within 4 weeks is a relative contraindication for lecanemab. Non-aspirin antiplatelets (clopidogrel, ticagrelor, etc.) and aspirin (up to 325 mg PO daily) are permitted;

1.2.6 Individuals' clinical features suggesting an alternative neurodegenerative disorder that is likely to be significantly contributing to primary neurological symptoms despite positive Alzheimer's disease biomarkers;

1.2.7 Individuals who meet clinical criteria for bvFTD[9], nfvPPA[10], svPPA[10], CBS[11], PSP[12], DLB[13], and FTD-ALS[14] should be excluded if, based on physician judgement, Alzheimer's disease is NOT likely to be contributing to their primary clinical phenotype;

1.2.8 Known history of a stroke clinical syndrome in the preceding 12 months;

1.2.9 Uncontrolled hypertension (blood pressure confirmed to be >165/100 on repeated measures at screening and potentially rescreening to rule out white coat syndrome;

1.2.10 History of endocrine disorders (such as diabetes or thyroid disease) that are currently poorly controlled (TSH above normal range, hemoglobin A1c > 9.0%);

1.2.11 History of seizure disorder during adulthood (even if well controlled);

1.2.12 Autoimmune or inflammatory disease that is not adequately controlled (i.e., patient is not compliant with appropriate therapy) or requires treatment with systemic immunosuppressive therapies discussed in exclusion criterion 1.2.21;

1.2.13 Recent cancer diagnosis not in remission (excluding skin cancers, localized prostate cancer);

1.2.14 Known HIV infection that is not being followed by a managing physician or not being treated via consistent compliance with antiretroviral therapy recommended by a managing physician;

1.2.15 Diagnosis of hemophilia or evidence of a bleeding disorder on testing (including a platelet count <50,000 or international normalized ratio [INR] >1.5);

1.2.16 Genetic conditions associated with increased risk of amyloid angiopathy which may pose a relative contraindication to treatment (e.g., trisomy 21, APP E693Q)

1.2.17 Major depression or other psychiatric illness that will interfere with comprehension of the requirements, potential benefits, and potential harms of treatment or participation in treatment;

1.2.18 Any other medical condition that may affect or be affected by lecanemab;

1.2.19 History of hypersensitivity to the anti-amyloid antibody under consideration;

1.2.20 Breastfeeding/lactation during treatment period;

1.2.21 Current use of immunomodulatory drugs including systemic corticosteroids, parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis. Systemic immunosuppressive drugs are not permitted for 3 months before starting anti-amyloid therapy, but may be considered on a case-by-case basis after starting therapy;

1.2.22 Use of another anti-amyloid antibody therapy in the last 6 months;

1.2.23 If, in the clinical opinion of the treating physician, the patient's primary care provider, or the Alzheimer's Infusion Core (AIC) board [discussed in section 2]), initiation or continuation of treatment of anti-amyloid therapy might pose a safety risk to the patient, the patient may also be excluded. Factors used to create a complete clinical picture of the patient for inclusion or exclusion of anti-amyloid therapy: CBC, CMP, TSH, B12, and coagulation studies within 3 months prior to treatment.

1.3 Ongoing Assessment of Exclusion Criteria

1.2. Patients and care partners will be instructed to inform the Alzheimer's Infusion Core (AIC) team managing anti-amyloid therapy if they meet exclusion criteria after initiating treatment with an anti-amyloid antibody therapy. The AIC will actively screen for treatment emergent adverse events (discussed in section 3.3.) that may meet exclusion criteria. Screening

for adverse events will also occur via collaboration with emergency medicine providers as discussed in section 4.1.1.3.

The managing AIC team will suspend anti-amyloid drug infusion orders if the patient meets exclusion criteria pertaining to anticoagulation, dual antiplatelet therapy, hypocoagulability, stroke, seizure, or intracranial lesions discussed in exclusion criterion 4 (with the exception of ARIA that meets criteria for continuation of therapy as outlined in section 4.3.1). Blood pressure will be assessed at the beginning of each infusion visit and anti-amyloid antibody infusions will not be initiated until the infusion nurse confirms systolic blood pressure ≤165 and diastolic blood pressure ≤100. AIC clinicians will use their clinical judgement in consultation with the AIC Board (discussed in section 2) to assess the potential safety risk if continued therapy in context of any other new medical diagnoses or adverse events that may satisfy other exclusion criteria for baseline initiation of therapy.

2. Description of a Specialized Alzheimer's Infusion Core (AIC) Service

At each UC medical center, clinical infusions with lecanemab and similar anti-amyloid therapies will be managed by a specialized clinical service, an AIC Service. Ordering privileges for anti-amyloid infusion treatment plans at each center will be restricted to a prespecified team of providers associated with an AIC. While patients are required to be clinically co-managed by a referring dementia specialist, the AIC team will be responsible for finalizing assessment of treatment eligibility, entering lecanemab treatment plan orders, managing follow-up safety MRI orders, and managing adverse events related to lecanemab, such as amyloid-related imaging abnormalities (ARIA). The AIC team will be comprised of supervising physicians (MDs or DOs) with expertise in dementia management and may include nurse practitioners (NPs) and delegated physician trainees (such as neurology residents and fellows). Neuroradiologists will be included as needed to evaluate eligibility or continued treatment decisions that are based on MRI findings (e.g., ARIA severity). The AIC will include one or more pharmacists to advise the clinician team.

2.1. AIC Board (to Review Treatment Eligibility)

Each medical center will form an AIC Board, consisting of AIC clinical providers, AIC support staff, and additional multidisciplinary Alzheimer's disease experts affiliated with the respective medical center, including representatives from pharmacy. The AIC board will meet every 2–4 weeks to discuss recent referrals to the AIC for lecanemab treatment. This board will review each patient's inclusion/exclusion criteria and consider any potential barriers to care (including financial burden or likelihood to comply with follow-up plan) before making the final decision about eligibility for treatment. The AIC board will also provide consultation for determining the timing of treatment cessations (discussed in section 5.2). Additionally, the AIC board will be responsible for complying with local institution requirements detailing the reporting of treatment-emergent adverse events (TEAE) (including ARIA and suspected infusion reactions) to the local institution medication safety officer and Pharmacy and Therapeutics (P&T) Committee. Screening for AEs is further discussed in section 3.3 (with specific discussion of infusion reactions in section 3.2.3 and ARIA in section 4).

2.2. The Process of Referrals to the AIC Services

We recommend a dedicated pipeline in which patients first establish care with a dementia specialist (preferably at the corresponding UC medical center) and then receive an AIC referral from their managing dementia specialist (or from their PCP in coordination with a dementia specialist, depending on insurance coverage). The source of patient referrals will, however, be left to the discretion of individual medical centers. Additionally, a prescreening process is recommended to review the appropriateness of each referral and the availability of data pertinent to the inclusions/exclusion criteria, prior to initial clinical assessment by an AIC clinical provider.

We recommend referrals be initiated via a specialized electronic medical record order which the referring dementia expert attests to the following:

- ☐ They will continue to co-manage their patient clinically
- ☐ The patient is over 40 years old with a clinical syndrome consistent with mild (CDR 0.5 to1) symptomatic Alzheimer's disease
- ☐The patient has objective evidence of brain amyloid beta deposition confirmed via one of the following:
    - ☐Amyloid PET
    - ☐ CSF evidence from a CLIA-approved lab
- ☐ The patient does not meet exclusion criteria based on recent MRI.
- ☐ The patient is not at an increased risk of hemorrhage (e.g., they are not on anticoagulation therapy)
- ☐ The patient meets criteria for treatment with anti-amyloid monoclonal antibody therapy to the best of the provider's knowledge.
- ☐ The patient has a recent MRI (≤12 months prior to treatment), recent lab testing (≤3 months prior to treatment) with CBC, CMP, TSH, B12, and coagulation studies (PT/INR, aPTT), and previous testing for APOE genotyping.

2.3. Clinic Call Coverage

An AIC physician (MD, DO) or nurse practitioner (NP) will be assigned to cover a call pool 24 hours per day, seven days per week, to assist in acute management of suspected adverse events (including ARIA) in the emergency department. Call coverage may be delegated to representatives from vascular neurology or a general neurology, provided the covering neurologist has been trained by the AIC to manage acute complications of anti-amyloid therapy, including ARIA. Depending on institution policies an on-call resident or fellow (MD, DO) may assist in call pool coverage and triage calls for an attending clinician. The call pool will also include a backup AIC clinician (MD, DO, or NP) to cover calls in case the first call person cannot be reached.

During business hours the on-call AIC clinician will urgently respond to infusion-center nursing staff for acute issues that arise during infusions.

During business hours, evenings, and weekends, the on-call AIC clinician must be available to respond to calls from AIC patients and their outside clinicians with concerns for symptoms potentially attributable to amyloid related imaging abnormalities (ARIA), as discussed in section 4.1. Patients will be given strict instructions to seek emergency medical care and not delay for AIC call-back under specific circumstances outlined in section 4.1.1. As discussed in section 4.1.1, each patient will be given contact information for the AIC call pool to facilitate urgent communication between the AIC and outside clinicians (typically emergency room physicians) managing their care. This contact information will also enable the patient and AIC team to facilitate prompt follow-up for all concerns potentially related to ARIA, regardless of whether they meet emergency room criteria outlined in section 4.1.1. An AIC provider must return all calls within the same day, and calls from emergency medical services must be returned urgently.

3. General Treatment Procedures:

A schedule of treatment events is contained in **Appendix A**.

3.1 Initial Screening

Initial screening is recommended to include multi-tiered visits involving a focused history, focused physical exam, review of concomitant medications, and a focused review of relevant laboratory and imaging data. Core procedures (performed by AIC team) for each screening visit will include

- **Screening clinic visit 1 (completed by nurse practitioner or physician)**
  - Initial review of inclusion/exclusion criteria.
  - Finalize any additional work up if needed, including APOE allele testing if previous eligible data is not available for screening.
  - Provide initial education for anti-amyloid antibody therapy including discussion of the mechanism of action, expectations of efficacy[15,16], ARIA risk (by APOE genotype), long term treatment schedule, and ARIA monitoring plan.

- **AIC Board (see section 2) review meeting**
  - Final review and determination of eligibility for treatment.
  - Initiate insurance prior authorization for anti-amyloid antibody therapy treatment, infusion center visits, and monitoring MRIs.

- **Screening clinic visit 2 (completed by physician)**
  - Final review of inclusion/exclusion criteria.
  - Disclosure of APOE status (if not previously performed) and reiteration of relative ARIA risk.
  - Obtain informed consent (discussed in Appendix D) for anti-amyloid antibody treatment.
  - Finalize infusion center and MRI orders and scheduling.

- Education about prohibited medication (Appendix E) including anticoagulation and tPA (or other thrombolytics). Education will include strong recommendations that patients wear a medical bracelet designating they must not receive tPA due to the associated mortality risk

3.2. Treatment Procedures

Patients who provide informed consent and meet inclusion/exclusion criteria may receive treatment with anti-amyloid therapy under observation at a designated UC infusion center with nursing staff on site (with ACLS certification and access to appropriate resources to acutely manage anaphylaxis).

Treatment procedures (including infusion orders and nursing orders dictated below) will be ordered by the AIC core physicians (with the assistance of local pharmacy) via a unified treatment plan, to facilitate regular infusions that align with timed clinical, laboratory, and imaging assessments (outlined in the Appendix A Schedule of events).

3.2.1. Dosing Schedule

Lecanemab: The FDA recommended dosage of lecanemab is 10 mg/kg, administered as an intravenous infusion over approximately one hour, once every two weeks. The infusion duration should not exceed 2 hours. The FDA label does not recommend titration of lecanemab.

3.2.2. Overall Infusion Visit Protocol

Treatment will be ordered by an AIC clinician via a local "treatment plan" devised with the local pharmacy. This treatment plan will include orders for recurring infusions, timed with necessary recurring safety imaging, laboratory, and clinical assessments.

- **Infusion timing**
  - **Lecanemab** will be administered as an intravenous (IV) infusion (10mg/kg) over approximately one hour every 2 weeks (+/- 8 days) and at least 7 days apart (See **Appendix B** for dilution and administration details).

- Infusion visits will begin with collection of weight (for calculations of dose) and vital signs including resting (after 5 minutes of sitting or reclining quietly) blood pressure and heart rate.

- **Safety MRIs:** Infusion visits may not proceed unless a physician has reviewed preceding safety MRI studies and verified that the patient is safe to proceed under ARIA management guidelines (section 4.3). Safety MRIs will occur before the 1st, 5th, 7th, and 14th infusions, at 52 weeks, and before annual follow up visits (as discussed in section 4.2 and **Appendix A**).

- **Observation (harmonized with current appropriate use recommendations)[1]:** Patients who receive lecanemab must undergo a 3-hour observation period after their first infusion for signs of hypersensitivity. Telephone follow up is recommended the same day of the 1st infusion, given the possibility of delayed infusion reactions. The observation period may then be reduced to 2 hours for the 2nd and 3rd infusions, and 30 minutes for subsequent infusions if no infusion reactions are observed or infusion reactions can be prevented with prophylaxis, and it is judged medically safe by the supervising AIC provider.

- Lecanemab infusions will be promptly halted upon the first observation of any signs or symptoms consistent with a greater than mild infusion reaction, and appropriate therapy will be initiated (Section 3.2.3).

- **EMERGENCY medications for acute hypersensitivity/allergic reaction:** For every infusion, have the following medications must be available at the infusion center and checked prior to infusion:

    - Albuterol inhaler 90 mcg/puff: 2 puffs inhaled x 1 dose PRN SOB or chest tightness.
    - Epinephrine 1:1000 (1mg/ml) 0.3 mg/0.3ml IM x 1 dose PRN anaphylaxis.
    - Diphenhydramine 50 mg IV x 1 dose PRN urticaria, pruritis, or SOB.
    - Hydrocortisone 100 mg IV x 1 dose PRN urticaria, pruritis, or SOB.
    - Acetaminophen 650 mg PO to 1 g x 1 dose PRN urticaria, pruritis, or SOB.

3.2.3. Treatment of Infusion Reactions

Infusion-related reactions are the most common side effect of lecanemab and should be expected in 20–30% of patients[16], particularly after the first infusion. Common symptoms of infusion-related reactions included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation. About 96% of infusion reactions are expected to fit within range of mild to moderate[16] (as defined in section 3.1.3.1).

3.2.3.1. Acute Management of Infusion Reactions

Management of lecanemab infusion reactions will differ by severity as graded by NCI-CTCAE, Version 4.0, grading of allergic/hypersensitivity reactions.

- **Grade 1 (Mild):** For mild reactions, interruption of lecanemab drip is not necessary and intervention not required unless judged necessary by the clinician.

- **Grade 2 (Moderate):** Moderate infusion reactions include symptoms that require interruption of lecanemab drip but are promptly responsive to treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, IV fluids). Moderate infusion reactions should be managed as follows:

- Stop the infusion.
- Administer one or more of the following under physician's clinical judgement
  - Diphenhydramine 50 mg IV x 1 dose PRN urticaria, pruritis, or SOB.
  - Hydrocortisone 100 mg IV x 1 dose PRN urticaria, pruritis, or SOB.
  - Acetaminophen 650 mg PO to 1 g x 1 dose PRN urticaria, pruritis, or SOB.
- Monitor for worsening of condition.
- Contact clinician on call.
- If the infusion reaction improves or resolves, infusion may be resumed based on the clinical judgement of the supervising physician (outlined in section 3.2.3.2).

- **Grade 3 (Severe):** Anaphylaxis and other severe infusion reactions include symptoms that are prolonged (not rapidly responsive to symptomatic medications or brief interruption of infusion), recur following initial improvement, require hospitalization, or result in clinical sequelae. Management for severe infusion reactions is as follows:
  - Stop the infusion and disconnect the infusion tubing from the subject.
  - Administer Epinephrine 1:1000 (1mg/ml) 0.3 mg/0.3ml IM x 1 dose PRN if anaphylaxis is suspected.
  - Administer one or more of the following under physician's clinical judgement
    - Diphenhydramine 50 mg IV x 1 dose PRN urticaria, pruritis, or SOB.
    - Hydrocortisone 100 mg IV x 1 dose PRN urticaria, pruritis, or SOB.
    - Acetaminophen 650 mg PO to 1 g x 1 dose PRN urticaria, pruritis, or SOB.
  - Administer bronchodilators for bronchospasms.
  - Administer IV fluids for hypotension.
  - Monitor for worsening of condition.
  - Contact AIC clinician on call.
  - Hospital admission for observation may be indicated based on physician judgement, particularly if anaphylaxis is suspected.
  - The patient will be permanently discontinued from all future treatment with lecanemab.

- **Grade 4:** Life-threatening consequences of infusion reactions (e.g., anaphylactic shock requiring pressors or respiratory mechanical ventilation) require immediate transfer to an emergency room or ICU for immediate stabilization (in addition to the acute management outlined for Grade 3 reactions). The patient will be permanently discontinued from all future treatment with lecanemab.

3.2.3.1. Resumption of Infusions After Infusion Reactions

- **Resumption of infusion the day of a Grade 1–2 infusion reaction:** If a patient experiences a **Grade 1** or **Grade 2** infusion reaction and their infusion is paused, the infusion may be resumed based on the clinical judgement of the supervising physician. If the infusion is resumed after a Grade 2 infusion reaction, it should be given at 50% of the prior rate once the infusion reaction has resolved. The infusion duration should not exceed 2 hours. Infusions may not resume after a **Grade 3** or greater infusion reaction.

- **Precautions for subsequent infusions:** For subsequent infusions (for the first follow-up infusion visit after a documented infusion reaction) the physician should consider premedicating the patient with diphenhydramine hydrochloride 25 to 50 mg (PO or IV), Hydrocortisone (100 mg IV), and acetaminophen 650 mg to 1 g orally. Use of corticosteroids for premedication should be done with caution. The physician should consider administering lecanemab infusions at 50% of the original study rate (but not alter the overall dose of 10mg/kg). If a patient does not experience infusion reactions upon the next several administrations, the physician may stop premedicating the subject and may increase the infusion rate to 10 mg/kg/1hr for subsequent infusions.

3.2.4. Treatment Resumption After Missed Doses

If an infusion is missed, the patient will resume treatment at the same dose as soon as possible. Subsequent infusions of lecanemab are to be administered every 2 weeks (+/- 7 days) and at least 14 days apart.

3.3. Monitoring for Treatment Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) that emerged during treatment with an anti-amyloid antibody (having been absent prior to treatment initiation).

The AIC board will be responsible for complying with local institution requirements detailing the regular reporting of treatment-emergent adverse events (TEAE) (particularly ARIA and suspected infusion reactions) to the local institution medication safety officer and Pharmacy and Therapeutics (P&T) Committee. AIC members will also ensure adherence to TEAE reporting requirements for patient treatment registries used to obtain prior authorization for treatment coverage (including the CMS for National Patient Registry or alternative registries approved by CMS, such as ALZ-NET).

Patients and care partners will be instructed to inform the Alzheimer's Infusion Core (AIC) team of TEAEs experienced by the patient. Screening for the most commonly expected adverse events will be conducted as outlined in sections 3.2.2 (pertaining to infusion reactions) and section 4 (pertaining to ARIA). The treating AIC clinician will actively screen for potential TEAEs via regular clinic follow up visits (including assessment of interim medical history and concomitant medications), safety labs, and safety imaging (as outlined in the schedule of events in Appendix A). Screening for adverse events will also occur via collaboration with emergency medicine providers as discussed in section 4.1.1.3.

Drug stopping parameters pertaining to TEAEs are further discussed in sections 1.3 (discussing new diagnoses that meet treatment exclusion criteria), section 3.2.3 (detailing management of infusion reactions), and section 3.3 (detailing ARIA management).

3.4. Flagging Anti-Amyloid Treatment in the Health Record

Treatment with tissue plasminogen activator (tPA) and other thrombolytic (clot-busting) drugs is absolutely contraindicated in patients who receive anti-amyloid antibodies given the high risk of mortality associated with concomitant use.[1]

Initiation of anti-amyloid therapy treatment must be immediately denoted in the patient's electronic health record and flagged as an absolute contraindication to thrombolytic medications (including tPA). The system of flagging the patient health record may be institution dependent, but it must ensure the following:

1) Relevant pharmacy, neurology, and emergency medical services will be made immediately aware of the patient's contraindication to tPA (and other thrombolytic drugs).
2) The patient is barred from use of tPA (and other thrombolytic drugs) in the instance of an acute stroke.

AIC providers will also recommend consideration of a medical bracelet and a care plan document each patient can use to alert outside medical providers to their contraindication to tPA and similar drugs (in the event the patient presents with a stroke syndrome to an outside medical hospital without access to their health record).

The clinical work flow in the acute care setting is further discussed in section 4.1.1.3.

4. Monitoring for Amyloid Related Imaging Abnormalities (ARIA)

4.1. Initial ARIA Symptom Screening

During collection of consent patients will be counselled about the typical symptoms of ARIA. After treatment is initiated, patient symptom screening will include discussion of the following potential symptoms:

- Headache
- Confusion
- Dizziness
- Nausea
- Fatigue
- Visual changes
- Gait disturbance
- Focal neurologic signs/symptoms referable to the involved area
- Seizure

Informed consent and subsequent clinical follow up will included reiteration of prohibited medications (Appendix E) including anticoagulation and thrombolytic medications (including tPA).

4.1.1. Responding to Treatment-Emergent Symptoms:

4.1.1.1. AIC Call-Pool Contact

Each patient will be given contact information for the AIC call pool to be used for the following purposes to facilitate urgent communication between the AIC and outside clinicians (typically emergency room physicians) managing their care. Patients will be given contact information to promptly contact an AIC provider in the event of potentially referrable to ARIA occur (discussed in section 4.1.). An AIC provider must return all calls within the same day, and calls from emergency medical services must be returned urgently. The on-call provider will then use their own medical judgement to determine if an ED referral and/or STAT head imaging is necessary.

4.1.1.2. Patient Emergency Room Instructions

Patients will be instructed to urgently seek emergency medical care (and not delay for AIC call back) in the event of acute/subacute neurological symptoms including severe headache, confusion, seizure, or focal neurological symptoms consistent with a TIA/CVA syndrome. The patient will be instructed to supply the managing emergency medical team the AIC clinic contact information to coordinate care. Any acute/subacute neurological symptoms will require stat MRI as discussed in section 2.1.2.

4.1.1.3. Acute Care/Emergency Room Workflow

The AIC core service will conduct training seminars for the other local medical center clinical services that are likely manage ARIA in an acute care setting, specifically including emergency medicine services and neurology services that are likely to interface with the ED for acute ARIA assessment (including vascular neurology and general neurology depending on the workflow of the institution and delegation of AIC call coverage discussed in section 2.3.).

The following minimal care plan is recommended for patients who present to the emergency department (ED) with suspected ARIA (including symptoms discussed earlier in section 4.1. that are not well explained by a preexisting condition).

- **Formal Consultation from Neurology** (specifically the serviced delegated to cover AIC ED call as discussed in section 2.3).
- **MRI to screen for ARIA.** The protocol must include FLAIR, DWI, and heme (GRE/SWI) sequences. Patients with suspected ARIA symptoms should not be discharged from the ED without MRI unless it is deemed appropriate by formal neurology (AIC call team) consultation and a STAT outpatient MRI has been assured.
- **Identification of absolute contraindication for tPA and other thrombolytic drugs.**
- **Communication of any detected TEAE (including ARIA) to outpatient AIC clinical service** (to facilitate halt in outpatient infusion orders if appropriate).

Head computed tomography (CT) is not appropriate to screen for ARIA, though initial CT screening will be performed for patients who otherwise meet existing acute care criteria for STAT head CT (e.g., patients who meet stroke code criteria or raise suspicion for subarachnoid hemorrhage).

4.1.2. Clinical Safety Follow-Up

In order to maintain continuity of care, adequately maintain treatment expectations, and screen for potential emergent symptoms, regular focused AIC continuity clinic visits will be scheduled with the following frequency:

- **Prior to (within 2 weeks of) the 5th infusion**: approximately 8 weeks (2 months) after the first infused dose.
- **Prior to (within 2 weeks of) the 7th infusion**: approximately 12 weeks (3 months) after the first infused dose.
- **Prior to (within 2 weeks of) the 14th infusion**: approximately 26 weeks (6–7 months) after the first infused dose.
- **Every 5–6 months thereafter**

Follow-up visits may be conducted by an AIC clinician, including a physician, NP, or designated trainee under the supervision of an attending physician. During follow-up visits, patients will undergo a focused history and physical exam, including screening for ARIA-related symptoms. The list of concomitant medication will be reviewed, and patients will be counseled about prohibited medications (anticoagulation and tPA).

Additional safety follow up will included safety laboratory studies (including but not limited to CBC with differential and coagulation studies [PT/INR, aPTT]) every 6 months.

4.2. MRI Monitoring for ARIA

It is a priority for safety MRIs to consistently occur on a consistent 3T scanner. The protocol must include FLAIR, DWI, and heme (GRE/SWI) sequences (see **Appendix C**). Detection of subtle ARIA on MRI scans often requires a proficient radiologist with previous training and experience in detecting ARIA. Therefore, we recommend a centralized ARIA consultation service with experienced neuroradiologists.

Timing of Safety MRIs

- **Baseline**: ≤12 months prior to treatment as discussed in initial screening (this is an essential study designated within FDA label).
- **Prior to (within 2 weeks of) the 5th infusion**: approximately 8 weeks (2 months) after the first infused dose. This is an essential study designated within FDA label.
- **Prior to (within 2 weeks of) the 7th infusion**: approximately 12 weeks (4 months) after the first infused dose. This is an essential study designated within FDA label.

- **Prior to (within 2 weeks of) the 14th infusion**: approximately 26 weeks (6–7 months) after the first infused dose. This is an essential study designated within FDA label.

- **At week 52 and then annually after treatment initiation:** These studies are not required by the FDA label. However, these studies are consistent with the safety monitoring conducted in a phase 3 study of lecanemab[16] and are this recommended for long term clinical follow up.

- **PRN under additional physician guidance**
    - Stat MRI (within 48 hours) is needed for urgent symptoms including acute neurological symptoms and other symptoms potentially referable to ARIA (section 4.1.1.)
    - Follow-up MRIs recommended after ARIA is detected (discussed in section 4.3.2.)

4.2.2. Classification of ARIA Severity

ARIA will be classified by radiographic severity based on classification criteria contained within lecanemab's FDA label (**Table 1**). ARIA severity may be further triaged based clinical severity. Asymptomatic ARIA may be triaged differently than symptomatic ARIA as discussed in section 4.3.1. In cases with symptoms that are attributable to ARIA, management may differ depending on whether or not these symptoms are designated as severe. Clinically severe symptoms included seizure or symptoms that require hospitalization, cause incapacitation, increase risk of permanent deficits, and/or significantly impact a patient's activities of daily living.

Table 1: ARIA Classification Criteria

ARIA Type	**Radiographic Severity**		
	Mild	**Moderate**	**Severe**
ARIA-E (edema)	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity measuring >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H: Micro hemorrhage	≤4 new incident microhemorrhages	5 to 9 new incident microhemorrhage	10 or more microhemorrhages
ARIA-H Superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	>2 focal areas of superficial siderosis
ARIA-H:			
Macro hemorrhage			≥1 macro hemorrhage(s)

4.3. ARIA Management

4.3.1. Treatment Adjustment/Halting Parameters

1) **Patients may continue lecanemab treatment with increased surveillance (monthly clinical follow up and monthly safety MRIs until resolution of ARIA-E and stability of ARIA-H on consecutive images) under the following scenarios:**
    a. Asymptomatic and radiographically mild or moderate ARIA-H with microhemorrhage.
    b. Asymptomatic and radiographically mild ARIA-E.

2) **Patients must halt lecanemab treatment and receive increased surveillance (monthly clinical follow up and monthly MRI until resolution of ARIA-E, stability of ARIA-H, and no less than 90 days of surveillance have occurred) under the following scenarios:**
    a. Symptomatic ARIA-H *without* severe† symptoms provided it is radiographically mild or moderate.
    b. Symptomatic ARIA-E *without* severe† symptoms.
    c. Asymptomatic ARIA (E or H) that transitions to symptomatic ARIA (*without* severe† symptoms and/or radiographically severe features).

    Criteria to restart lecanemab discussed in section 4.3.4.

3) **Patients must permanently discontinue treatment with ongoing surveillance (monthly clinical follow up and MRI until resolution of ARIA-E, stability of ARIA-H, and no less than 90 days of surveillance have occurred) under the following circumstances:**
    a. Symptomatic or Asymptomatic radiographically severe ARIA-H (including macro hemorrhage).
    b. Severe† Symptomatic ARIA (E or H) (Note: In the most severe symptomatic ARIA, high-dose corticosteroid therapy should be considered as discussed in section 4.3.3).
    c. ≥3 episodes of ARIA (E or H) regardless of clinical or radiographic severity
    d. ARIA (E or H) accompanied by seizure.

† "Severe" ARIA symptoms will be defined as symptoms that are attributable to radiographically confirmed ARIA and involve seizure, require hospitalization, cause incapacitation, increase risk of permanent deficits, and/or significantly impact a patient's activities of daily living.

Table 2: Treatment Halting Parameters Based in ARIA Severity

<table>
<tr><th rowspan="3">Clinical Symptom Severity</th><th colspan="4">Radiographic Severity</th></tr>
<tr><th>Mild</th><th>Moderate</th><th colspan="2">Severe</th></tr>
<tr><td>ARIA-E & H</td><td>ARIA-E & H</td><td>ARIA-E</td><td>ARIA-H
or Macrohemorrhage</td></tr>
<tr><td>Asymptomatic</td><td><u>Continue Dosing</u> with increased surveillance (defined in section 4.3.2.)</td><td colspan="2" rowspan="2"><u>Suspend Dosing</u> with increased surveillance (defined in section 4.3.2.). Once ARIA-E is resolved <u>AND</u> ARIA-H is stable, the patient may resume dosing at the same dose.</td><td rowspan="2"><u>Permanently Discontinue Dosing</u>* with increased surveillance (defined in section 4.3.2.)</td></tr>
<tr><td>Mild to Moderate</td><td></td></tr>
</table>

Severe†	Note: In the most severe symptomatic ARIA, high-dose corticosteroid therapy should be considered as discussed in section 4.3.3.

† "Severe" ARIA symptoms will be defined as symptoms that are attributable to radiographically confirmed ARIA and involve seizure, require hospitalization, cause incapacitation, increase risk of permanent deficits, and/or significantly impact a patient's activities of daily living.
* ≥3 episodes of ARIA or seizure should trigger permanent discontinuation.

4.3.2. Follow-up after ARIA is Detected

After ARIA is detected, scheduled follow up will be conducted every month (4 weeks +/- 7 days) until ARIA-E resolves and ARIA-H has stabilized. This period of increased monitoring should occur no less than 90 days. Additional ad hoc follow up may be considered as discussed in section 4.1.1. Scheduled post-ARIA follow up will include:

- **Monthly Clinical** visits (telemedicine when deemed appropriate by MD) to review ARIA symptoms and conduct a focused neurological exam.
- **Monthly Safety MRI** preferably on a consistent 3T scanner. The protocol must include a FLAIR, DWI, and heme sequence (SWI, T2*, GRE).

4.3.3. Additional ARIA Management Considerations

- **Blood Pressure Assessment:** Assessment of blood is recommended as soon as ARIA is identified (as ARIA may be complicated by malignant hypertension). Blood pressure should also be reassessed in patients with radiographic or clinical features of ARIA which fail to improve after drug suspension.

- **High dose corticosteroids:** Treatment with high-dose systemic corticosteroids should be considered in patients with radiographic or clinical features of ARIA which fail to improve after drug suspension, require hospitalization, or raise concern for permanent deficits.
    - A typical regimen may include methylprednisolone 1gm intravenously per day for 5 days followed by oral prednisone, 60 mg per day, slowly tapered over weeks or months.
    - Prior to treatment, lumbar puncture (LP) may be used to screen for an aseptic inflammatory CSF pattern (high protein, normal white count), if brain MRI does not suggest contraindication to LP.

- **Seizure Management:** Seizure surveillance is recommended for clinically severe ARIA as defined in section 4.2.2. EEG is strongly recommended for patients with recurrent, transient, or fluctuating neurological symptoms with confusion or focal features.
    - AED therapy (Keppra preferred) will be initiated if seizure is confirmed on EEG.
    - Empiric AED therapy may also be considered in the following scenarios:
        - Epileptiform discharges on EEG in a brain region referable to the patient's syndrome.
        - Recurrent stereotyped semiology concerning for seizure which did not co-occur with EEG studies to date.

4.3.4. Reintroduction of Lecanemab after ARIA

4.3.4.1. Criteria for Reintroduction of Therapy

Patients who met criteria for temporary drug suspension (Section **4.3.1., Table 3**) may consider restarting lecanemab therapy with caution if ALL the following criteria are met:

- ARIA-E has resolved on follow-up safety MRI scan (between 2 scans ≥ 1 months apart).
- ARIA-H has stabilized (both in terms of lesion size and number) on follow-up safety MRI scan (between 2 scans ≥ 4 weeks apart).
- Any symptoms attributable to ARIA have resolved.
- Reintroduction of lecanemab therapy (as a result of ARIA) will occur no more than 2 times.

4.3.4.2. Protocol for Lecanemab Reintroduction

After criteria for in reintroduction of therapy are met, dosing may resume at that same dose and titration schedule as discussed in section (3.2.1. and 3.2.2.).

- Clinic follow-up and repeat safety MRI is recommended approximately 6 weeks after resumption of therapy).
- Patients will otherwise resume the same schedule of clinic visits and safety MRIs outlined in sections 4.1.2. and 4.2.1.

5. Monitoring Drug Efficacy

5.1. Data Collection

There are no currently validated measures to trend lecanemab efficacy in individual patients. To improve future clinical practice, all patients will be encouraged to take part in a separate IRB-approved longitudinal research study protocol (such as the ALZ-NET [Alzheimer's Network for Treatment and Diagnostics] protocol or other local protocols at their institution) to collect clinical data, imaging data, and biospecimens created during treatment.

5.1.1. Clinical Data Collection

Phase 3 trials of lecanemab utilized primary and secondary clinical measures that may not be easy to operationalized for consistent collection in clinic-based patient cohort. For this reason, patients treated with lecanemab will undergo a minimal battery of regular assessments with clinical tools that are either easy to obtain via a tablet-based platform, easily to obtain as a caregiver/patient questionnaire, or already clinically ubiquitous. Clinical assessments will occur either annually (for cognitive measures with a possible practice effect) or every ~6 months (for questionnaires)

- **Suggested Annual Assessments** (conducted screening visit 2 and then annually thereafter)

  - MMSE[6] or MoCA[8] (required for ALZ-NET)
  - AD8 (required for ALZ-NET)
  - FAQ (optional for ALZ-NET)
  - NPI (optional for ALZ-NET)
  - Expanded Cognitive Battery: Additional assessments may include other neuropsychological batteries that may be easily administered and harmonized across multiple clinical settings, such as the UCSF Brain Health Assessment[17]. We recommend a battery with at least one formal measure of verbal memory (such as a list learning task).
- **Suggested Semi Annual Assessments** (conducted screening visit 2, week 26 clinic visit, and then every 6–12 months thereafter)
  - Functional Activities Questionnaire (FAQ)[18]
  - Clinical Dementia Rating Scale (CDR)[5] (optional study that is only collected if it is feasible)
  - Zarit Caregiver Burden Interview (ZBI)[19]
  - Quality of Life in Alzheimer's disease scale (QoL-AD)[20]
- NOTE: ALZ-NET requires MMSE or MoCA. AD8, FAQ, and NPI are optional. ALZ-NET assessments are q6 months x 2 years, then annually.

5.1.2. Biospecimen Collection

Patients who consent to biospecimen collection may undergo plasma collection at baseline and roughly 6-month intervals (described in appendix A) provided that plasma collection and storage will occur under a separate IRB-approved research protocol (such as the ALZ-NET [Alzheimer's Network for Treatment and Diagnostics] protocol or other local protocols at their institution).

5.1.3. Neuroimaging Data Collection

- **MRI:** Clinical baseline screening and follow-up safety MRI (described in section 4.2.) may be harmonized with the ADNI (Appendix C), to enable future collection of a harmonized imaging data set for patients consenting to future research.

- **Amyloid and Tau PET:** Clinical follow up will not initially require PET studies, but the AIC will make every effort to coordinate with observational research projects at UC that may co-enroll patients and enable follow-up PET studies. Alternatively, follow-up clinical PET imaging may be pursued if updates to insurance reimbursement policies permit serial PET imaging, particularly if amyloid PET is validated as means of determining anti-amyloid antibody treatment duration.

5.2. Concluding Treatment with Lecanemab

Lecanemab's possible efficacy signal and safety profile are only well understood in individuals with mild cognitive impairment or mild dementia treated over about 18 months. Discontinuation of lecanemab should be considered in any patients who progress to a moderate or greater stage of dementia (CDR[5] global score ≥2), in which has lecanemab has no available efficacy data. A moderate stage of dementia may include loss of independence outside of the home, retention of

only simple home chores, and/or need for assistance with some personal care tasks. The AIC clinical team (in consultation with the patients treating dementia specialist and ordering provider) will assess the appropriateness of ongoing treatment every 6–12 months after the first year of treatment. (See section 4.3.1. regarding stopping guidelines pertaining to ARIA.)

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Appendix A: Schedule of Events

Week (+/- 8 days)	Screening[a]	1	3	5	7	8	9	11	12	13	15	17	19	21	23	25	26	27	29	31	33	35	37	39	41	43	45	47	49	51	52	53	Long term
Dose number		1	2	3	4		5	6		7	8	9	10	11	12	13		14	15	16	17	18	19	20	21	22	23	24	25	26		27	
Outpatient Clinic Visit	X					X			X								X														X		Q 6 months
Informed consent[b]	X																																
Focused history & physical exam	X					X			X								X														X		Q 6 months
Concomitant medications[b]	X					X			X								X														X		Q 6 months
Confirmation of Clinical Diagnosis	X																																
Confirmation of AD biomarkers	X																																
APOE allele testing[c]	X																																
Safety labs[d]	X					X			X								X														X		Q 6 months
Inclusion/ exclusion & review treatment appropriateness	X					X			X								X														X		Q 6 months
Weight (before dose)		X	X	X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	Q 2 weeks
Vitals (before dose)		X	X	X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	Q 2 weeks
Infusion Center Visit (lecanemab dosed 10mg/kg)		X	X	X	X		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	Q 2 weeks
Safety Brain MRI[e]	X					X			X								X														X[f]		Q 12 months[f]
MMSE and/or MoCA[g]	X																														X		Q12 months
Formal Cognitive Testing[h]	X																														X		Q 12 months
FAQ	X																X														X		Q 6 months
CDR[i]	X																X														X		Q 6 Months
ZBI	X																X														X		Q 6 Months
Qol-AD	X																X														X		Q 6 Months
Plasma collection[j]	X																X														X		Q 6 Months

4.2.Pre-referral procedures will typically be performed by the patient's managing dementia specialist (not necessarily the AIC team).

4.3. Discussion of concomitant medications will explicitly include discussion of prohibited medications such as anticoagulants and tPA.
4.4. While APOE allele testing will typically be performed prior to clinic referral, it may be initiated by an AIC provider during screening.
4.5. Screening safety labs include CBC, CMP, TSH, B12, and coagulation studies (PTT, PT/INR, platelets). Follow up safety labs will include (but need not be limited to) and CBC and coagulations studies
4.6. Baseline MRI must occur within 12 months of planned treatment start date.
4.7. Frequency of long tern safety MRI after dose 14 may be impacted by insurance reimbursement
4.8. MoCA may be done in lieu of the MMSE. The MMSE and MoCA do not need to be repeated during screening if they were performed by the managing clinician in the 3 months prior to screening.
4.9. Additional formal cognitive assessments may include other neuropsychological batteries that may be easily administered and harmonized across multiple clinical settings, such as the UCSF Brain Health Assessment17 or. We recommend a battery with at least one formal measure of verbal memory (such as a list learning task).
4.10. The CDR is optional if it cannot be easily obtained in the patient's clinical setting.
4.11. Plasma collection and storage is optional will occur if the patient consents to a separate IRB-approved research protocol.

Appendix B: Dilution and Administration Instructions

B.1 Dilution protocol:

- Prior to administration, LEQEMBI must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP.
- Use aseptic technique when preparing the LEQEMBI diluted solution for intravenous infusion.
- Calculate the dose (mg), the total volume (mL) of LEQEMBI solution required, and the number of vials needed based on the patient's actual body weight and the recommended dose of 10 mg/kg. Each vial contains a LEQEMBI concentration of 100 mg/mL.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check that the LEQEMBI solution is clear to opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Remove the flip-off cap from the vial. Insert the sterile syringe needle into the vial through the center of the rubber stopper.
- Withdraw the required volume of LEQEMBI from the vial(s) and add to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
- Each vial is for one time-use only. Discard any unused portion.
- Gently invert the infusion bag containing the LEQEMBI diluted solution to mix completely. Do not shake.
- After dilution, immediate use is recommended [see Description (11)]. If not administered immediately, store LEQEMBI refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours, or at room temperature up to 30°C (86°F) for up to 4 hours. Do not freeze.

B.2. Administration Instructions

- Visually inspect the LEQEMBI diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque or foreign particles are seen.
- Prior to infusion, allow the LEQEMBI diluted solution to warm to room temperature.
- Infuse the entire volume of the LEQEMBI diluted solution intravenously over approximately one hour through an intravenous line containing a terminal low-protein binding 0.2 micron in-line filter. Flush infusion line to ensure all LEQEMBI is administered.
- Monitor for any signs or symptoms of an infusion-related reaction. The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids (see section 3.2)

B.3 Dosage Forms and Strengths

LEQEMBI is a clear to opalescent and colorless to pale yellow solution, available as:

- Injection: 500 mg/5 mL (100 mg/mL) in a single-dose vial
- Injection: 200 mg/2 mL (100 mg/mL) in a single-dose vial

Appendix C: ADNI3 MRI Protocol Parameters

Sequence Name	Geometry (FOV @ reconstructed resolution) in mm	Timing Parameters in ms	Approx. run time in minutes
MP-RAGE	208x240x256mm @1x1x1mm	TE=min full echo TR=2300 TI=900	6:20
3D FLAIR	256x256x160mm @1.2x1x1mm	TE=119 TR=4800 TI=1650	5:30
T2* GRE	220x220x176mm @0.85x0.85x4mm	TE=20 TR=650	4:10
Diffusion	ADNI-3 Basic 232x232x160mm @2x2x2mm	TE=56 TR=7200	7:30

***Note: SWI is preferred over T2* clinically, but if SWI is not possible clinical sites may consider harmonizing heme sequencing with ADNI protocol as described above to enable future comparisons in a unified data set.**

Appendix D: Informed Consent Considerations

Each UC clinical site will create their own informed consent form (ICF) documents, with consideration of local requirements, local clinical practice, and consensus guidance statements from experts in the field of neuro-ethics[21]. We recommend informed consent procedures for lecanemab contain a discussion of the following minimal components.

- Education about thee modest efficacy signal associated with lecanemab treatment in the phase 3 clinical trial[16]. We recommend setting clear expectations that lecanemab is only expected to slow clinical decline, not halt decline or improve symptoms.

- Education about adverse reactions commonly associated with lecanemab infusions, such as infusion reactions and the Amyloid Related Imaging Abnormalities (ARIA), including ARIA-E and ARIA-H. The discussion of possible ARIA symptoms may include the following:
    - Headache
    - Confusion
    - Dizziness
    - Nausea
    - Fatigue
    - Visual changes
    - Gait disturbance
    - Focal neurologic signs/symptoms referable to the involved area
    - Seizure

- A thorough discussion of the patient's unique risk of ARIA based on their APOE allele status[16], tailored to whether or not they are an ε4 non-carrier, ε4 heterozygote, or ε4 homozygote. Discussion should cover the unique risk of ARIA-E, ARIA-H, symptomatic ARIA, and severe ARIA.

- A thorough discussion of contraindicated medications, including a discussion of anti-coagulation and a discussion about the absolute contraindication for tPA (due to its mortality risk). This discussion should reference that lecanemab treatment may exclude patients from receiving tPA or other thrombolytics for acute stroke or myocardial infarction. Patients should be strongly encouraged to wear a medical bracelet designating that they must not receive tPA due to the associated mortality risk (in order to prevent unintended tPA administration if a patient is rendered unable to communicate).

- A discussion of the burden of treatment, including the necessary frequency of infusions and timing of required safety follow up clinical assessments and MRIs discussed in section 5.2.

- Discussion of the potential out-of-pocket financial burden associated with lecanemab treatment, including the cost of safety follow up.

- If pertinent, additional discussion about the limitations of efficacy and safety data for lecanemab treatment in individuals with a patient's unique demographic features.

Appendix E: Prohibited Medications:

Treatment with anticoagulants (DOACs, warfarin, lovenox, heparin, fondaparinux etc.) within 4 weeks is a contraindication for lecanemab. Non-aspirin antiplatelets (clopidogrel, ticagrelor, etc.) and aspirin (up to 325mg PO daily) are permitted. Patients who are expected to receive anticoagulation must discontinued lecanemab.

Treatment with tissue plasminogen activator (tPA) and other thrombolytic (clot-busting) drugs is strictly contraindicated in patients undergoing treatment with lecanemab given the potential increase in mortality risk. We recommend that patients wear a medical bracelet designating that they not receive tPA, to prevent accidental administration of tPA in the event they are unable to communicate their restrictions to emergency medical services. Anti-amyloid antibody treatment will also be flagged as a contraindication to thrombolytic drugs in the patient's electronic health record.

Current use of immunomodulatory drugs including systemic corticosteroids, parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis. Systemic immunosuppressive drugs are not permitted for 3 months before starting anti-amyloid therapy, but may be considered on a case-by-case basis after starting therapy.

Appendix F: Disclosures/Conflicts of Interest

UC Davis

- **Charles DeCarli, MD**, does not report any to relevant relationships/activities/interests that are related to the content of the UC anti-amyloid antibody protocol document.
- **Sarah Tomaszewski Farias, PhD**, does not report any to relevant relationships/activities/interests that are related to the content of the UC anti-amyloid antibody protocol document.
- **David Bissig, MD, PhD**, does not report any to relevant relationships/activities/interests that are related to the content of the UC anti-amyloid antibody protocol document.

UC Irvine

- **Claire Henchcliffe, MD, DPhil**, does not report any to relevant relationships/activities/interests that are related to the content of the UC anti-amyloid antibody protocol document.
- **Joshua D. Grill, PhD**, reports grant support from National Institute on Aging, Bright Focus Foundation, Eli Lilly, Eisai, Alzheimer's Association, Biogen, and Genentech. He has received consulting fees from SiteRx. He has received Support for attending meetings and/or travel from the Alzheimer's Association.
- **S. Ahmad Sajjadi, MD, PhD**, is PI of the R01 grant from NIA entitled "Diagnosis and risk factor of hippocampal sclerosis of aging; a common Alzheimer's mimic in the oldest old" R01 AG062706 and PI of the R21 grant from NIA entitled "Postmortem MRI for improving the diagnosis of Alzheimer's mimics in the oldest old", R21 AG075870 (payments made to institution). He reports ad hoc consulting work with Guidepoint 2022. He served on an advisory board for Eisai on May 21, 2022 and an advisory board for Genentech on October 12, 2022.

UC Los Angeles

- **Stanley Thomas Carmichael, MD, PhD**, does not report any to relevant relationships/activities/interests that are related to the content of the UC anti-amyloid antibody protocol document.
- **Keith Vossel, MD**, does not report any to relevant relationships/activities/interests that are related to the content of the UC anti-amyloid antibody protocol document.

UC San Diego

- **James B. Brewer, MD, PhD**, reports leadership in Alzheimer's Association San Diego/Imperial Valley Medical and Scientific Lead. He also reports stock or stock options in Human Longevity, Inc, Cortechs.ai, Enkephalos Inc, and ACLIP Inc.
- **Gabriel C. Léger, MD**, reports grand support from the NIH, P30-AG062429 (payments made to UCSD). He served on an Advisory Board for Eisai in July 2022 (payment made directly to him).

UC San Francisco

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UCSF Fresno

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