Clinical Trial Protocol: ALZ-2026-04

Study Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Alzene-101 in Patients with Early-Stage Alzheimer's Disease.

Sponsor: NeuroGen Therapeutics Global

Principal Investigator: [Your Name/Neurologist]

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1. Study Rationale

Alzheimer's Disease (AD) remains a critical unmet medical need.[1] Current therapies focusing on plaque removal have shown modest results. Alzene-101 is a novel humanized monoclonal antibody designed to selectively bind to and neutralize **soluble amyloid-beta oligomers**, which are hypothesized to be more neurotoxic than insoluble plaques.

2. Study Objectives

- **Primary:** To evaluate the change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score at 72 weeks.
- **Secondary:** To assess changes in cognitive function via ADAS-Cog14 and to monitor the incidence of Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H).[2]

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3. Patient Selection Criteria

The selection process is designed to isolate patients in the "prodromal" or "mild" stages of AD to ensure the brain tissue is still salvageable (neuroplasticity window).

3.1 Inclusion Criteria

To be eligible for participation, patients must meet **all** of the following:

1. **Age:** 55 to 85 years (inclusive) at the time of screening.
2. **Diagnostic Status:** Must meet the NIA-AA clinical criteria for Probable Alzheimer's Disease or Mild Cognitive Impairment (MCI) due to AD.

3. **Cognitive Scores:**
    - **MMSE:** Score between 22 and 30 (inclusive).
    - **CDR Global Score:** 0.5 or 1.0.
4. **Biomarker Confirmation:** Positive PET amyloid scan or cerebrospinal fluid (CSF) $A\beta_{42}/A\beta_{40}$ ratio consistent with amyloid pathology.
5. **Study Partner:** Availability of a reliable caregiver or partner who spends at least 10 hours/week with the patient and can accompany them to clinic visits.
6. **Stability of Medication:** If on cholinesterase inhibitors (e.g., Donepezil) or Memantine, the dose must be stable for at least 12 weeks prior to baseline.

3.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. **Non-AD Dementia:** Diagnosis of Vascular Dementia, Lewy Body Dementia, Frontotemporal Dementia, or normal pressure hydrocephalus.
2. **Neurological Comorbidity:** History of stroke, brain tumors, or epilepsy.
3. **MRI Contraindications:** Presence of pacemakers, metal implants, or claustrophobia that prevents high-resolution MRI monitoring.
4. **Cerebrovascular Risk:** * Evidence of >4 microhemorrhages on baseline MRI (T2* or SWI sequences).
    - History of major macro-hemorrhage or cortical infarct.
5. **Uncontrolled Medical Conditions:** Unstable cardiovascular disease, severe hepatic impairment, or poorly controlled Type 2 Diabetes ($HbA1c > 8.5\%$).
6. **Psychiatric Disorders:** Current clinical depression (Geriatric Depression Scale > 8) or history of schizophrenia/bipolar disorder.
7. **Blood Thinners:** Concurrent use of therapeutic anticoagulants (e.g., Warfarin, Rivaroxaban). Low-dose Aspirin ($\leq 100mg$) is permitted.

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4. Study Design and Methodology

4.1 Randomization

Participants will be randomized in a **1:1:1 ratio** to receive:

- **Group A:** Low-dose Alzene-101 (5 mg/kg IV every 4 weeks).
- **Group B:** High-dose Alzene-101 (10 mg/kg IV every 4 weeks).
- **Group C:** Placebo (Saline IV every 4 weeks).

4.2 Safety Monitoring (ARIA Protocol)

Because Alzene-101 targets amyloid, there is a risk of **ARIA (Amyloid-Related Imaging Abnormalities)**.

Visit Month	Procedure	Purpose
Month 0	Baseline MRI	Establish safety baseline
Month 3	Safety MRI	Monitor for early ARIA-E (Edema)
Month 6	Safety MRI	Dosage adjustment if microhemorrhage detected
Month 12	Mid-point MRI	Long-term safety assessment

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5. Statistical Analysis Plan

The sample size ($N=450$) is powered to detect a 25% slowing of decline in CDR-SB with 80% power at a significance level of $\alpha = 0.05$.

$$\text{Primary Endpoint Calculation: } \Delta CDR\text{-}SB = (Score_{Week 72} - Score_{Baseline})$$

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6. Ethics and Informed Consent

The study will be conducted in accordance with the **Declaration of Helsinki** and Good Clinical Practice (GCP) guidelines. Informed consent must be obtained from both the participant and their legally authorized representative (LAR).