The PROGRESS-AD Study

Participant Eligibility Checklist

Protocol Version: Amendment 02 (09 Jan 2025)

Site Number: _____

Principal Investigator: _____

Participant ID: _____

Inclusion Criteria Participants are eligible to be included in the study only if all of the following criteria apply:	Comments (if applicable)	Yes	No
Age **INC#1** Participant must be 50 to 85 years of age, inclusive, at the time of signing the informed consent.		☐	☐
Type of participant and disease characteristics **INC#2** The participant must be in the Alzheimer's continuum as defined by the 2018 NIA-AA Research Framework (See Section 10.9) [Jack , 2018] corresponding to the clinical categories of MCI due to AD and mild AD dementia. These categories include participants with positive biomarkers of AD pathophysiology along with a clinical spectrum ranging from subtle cognitive decline with no daily functional impact (MCI due to AD) up to participants with both clear cognitive decline and functional impact (mild AD dementia). The criteria require evidence of cerebral amyloidosis (A+) as detailed in the following: a. Positive PET result: Amyloid PET scans must be read by a central imaging lab. • Historical amyloid PET collected with a formal report prior to the start of screening may fulfill this criterion if it meets the requirements defined in the imaging charter of the central imaging laboratory after review by the medical monitor. • Any participant with a positive historical amyloid PET, who participates in the amyloid PET sub-study and found to have a negative amyloid PET at baseline, will be excluded from the study. If any participant with historical amyloid PET who participates in the CSF sub-study is subsequently found to have CSF Aß test result inconsistent with amyloid positivity, a new amyloid PET may be requested after discussion with the medical monitor, which if negative will lead to exclusion. b. Positive CSF result: CSF Aß test result indicative of amyloid positivity. • Historical CSF measurements collected prior to the start of screening with a formal report may fulfill this criterion after review by the medical monitor. If such a participant is subsequently found to have CSF Aß test result inconsistent with amyloid positivity, a new amyloid PET may be requested after discussion with the medical monitor, which if negative, will lead to exclusion. Such a participant, who takes part in the amyloid PET sub-study and is found to have negative amyloid PET at baseline, will be excluded from the study.		☐	☐

Amyloid elevation for study eligibility may require repeat assessment as outlined in Table 1 below.

Table 1 Amyloid Positivity Eligibility

Initial Confirmatory Test	Second Assessment, if Initial Test is Negative[1]
Historical positive amyloid PET	NA
Historical positive CSF amyloid test	NA
Study amyloid PET[1]	New study CSF testing
Study CSF testing	New study amyloid PET[1]

[1] The sponsor may decline performing a new amyloid PET or CSF if participant has a negative historical amyloid PET or historical CSF that was performed prior to the start of screening.

CSF = cerebrospinal fluid; PET = positron emission tomography.

INC#3 Prospective participants must also meet the following inclusion criteria to define clinical severity:

a. MMSE score of between 21 and 29 points, inclusive, at screening
b. CDR-GS of 0.5 to 1.0
c. CDR Memory Box score ≥0.5
d. Participants with objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the WMS-IV LMII:
    i. ≤15 for age 50 to 64 years
    ii. ≤12 for age 65 to 69 years
    iii. ≤11 for age 70 to 74 years
    iv. ≤9 for age 75 to 79 years
    v. ≤7 for age 80 to 90 years.

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INC#4 If the participant is receiving symptomatic AD medications such as an AChEI (e.g., donepezil, rivastigmine, galantamine) or memantine, the dosing regimen must have been stable for at least 12 weeks prior to screening and must not be expected to change during study participation.

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INC#5 If the participant is receiving other medications for AD-related symptoms or associated conditions (e.g., antidepressants, anxiolytics, hypnotics, antipsychotics), the dosing regimen must have been stable for at least 4 weeks prior to screening and not expected to change during study participation. Symptoms must be considered adequately and stably controlled by the investigator, without marked changes in medication anticipated for the duration of the study.

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Weight

INC#6 Body weight ≥45 kg to ≤120 kg with BMI between 17 and 34.9 kg/m^2, inclusive.

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Sex and contraceptive/barrier requirements **INC#7** A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies: Is a WONCBP as defined in Section 10.4.1.2 OR Is a WOCBP as defined in Section 10.4.1.1 and is using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.2 from at least 14 days prior to the first dose of study intervention until at least 12 weeks after the last administered dose of study intervention. • A WOCBP must have a negative, highly sensitive serum pregnancy test at Screening Visit 1 and a negative, highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Section 1.3. • Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. • The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention). • The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. **Note:** If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.		☐	☐
INC#8 Male participants are eligible to participate if they agree to the following during the study and for at least 12 weeks after the last dose of study intervention corresponding to time needed to eliminate study intervention (5 terminal half-lives) plus an additional 90 days (a spermatogenesis cycle): • Refrain from donating sperm. PLUS either: • Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent. OR • Must agree to use contraception/barrier if engaging in heterosexual intercourse with a woman of childbearing potential, as follows: • Agree to use a male condom; and • Female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.4.2.		☐	☐

Informed consent **INC#9** Willing and able to give informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Where local regulations permit inclusion of participants deemed not having capacity to provide informed consent, a legally authorized representative must provide informed consent on his or her behalf, and the participant must provide assent, in accordance with the local regulations, guidelines, and IRB/IEc. A participant's capacity to provide informed consent will be determined by the investigator in accordance with local regulations or guidelines.		☐	☐
Other inclusion criteria **INC#10** Availability of an adult person ("study partner") who, in the investigator's opinion, has frequent and sufficient contact with the participant (e.g., at least 8 hours per week of in-person contact), is able to provide accurate information regarding the participant's cognitive and functional abilities, agrees to provide information at clinic visits (only those visits which require study partner input for efficacy assessments), and signs the ICF of the study partner. • The study partner must have sufficient cognitive capacity, in the investigator's opinion, to accurately report on the participant's behavior, cognitive, and functional abilities throughout the study duration. This would require that the study partner is in sufficiently good general health, in the investigator's opinion, to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures. • Every effort should be made to have the same study partner participate throughout the duration of the study. If the initial study partner can no longer continue in the study, a replacement study partner meeting the same criteria must be available for the participant to continue in the study. • The study partner does not have to be living in the same residence with the participant. For such a study partner that does not reside with a participant, the investigator has to be satisfied that the participant can access or contact the study partner readily during the times when the study partner is not with the participant. If in doubt about whether a participant's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor for adjudication.		☐	☐
INC#11 Participant and study partner are fluent in the language of the COAs and PROs used at the study site as assessed by the investigator.		☐	☐
INC#12 In the investigator's opinion, participant has adequate visual and auditory acuity, with corrective lenses and hearing aids permitted, to perform the study procedures including the clinical scales.		☐	☐
INC#13 Participant is able to complete all aspects of the study (including MRI, LP [optional], blood draws, genotyping, and imaging, as applicable). Participants who are enrolled in sites that do not have tau/amyloid PET imaging available are not required to undergo these procedures, but amyloid positivity will need to be confirmed with CSF testing or historical CSF amyloid/amyloid PET reports. The participant should be capable of completing assessments either alone (all assessments) or with the help of the study partner (not permitted for cognitive assessments).		☐	☐
INC#14 Participant agrees not to donate blood or blood products for transfusion for the duration of the study and for 12 weeks after the last dose of study intervention.		☐	☐

Exclusion criteria Participants are excluded from the study if any of the following criteria apply:	Comments (if applicable)	Yes	No
Medical Conditions – CNS related. **EXC#1** Has evidence of any neurological condition other than AD that may contribute to cognitive impairment, including but not limited to frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Huntington disease, normal pressure hydrocephalus, hypoxic injury, seizure disorder, static encephalopathy, closed brain injury, intracranial neoplasm, or developmental disability.		☐	☐
EXC#2 History or presence of vascular disease that has the potential to affect cognitive function (e.g., clinically significant stenosis or plaque in the carotid or vertebral arteries, aortic aneurysm, aortic stenosis, intracranial aneurysm, macrohemorrhage, or arteriovenous malformation).		☐	☐
EXC#3 History or presence of stroke within the past 1 year or recent transient ischemic attack within 180 days before screening.		☐	☐
EXC#4 History of severe, clinically significant (e.g., persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion).		☐	☐
EXC#5 History or presence of intracranial tumor.		☐	☐
EXC#6 Presence of ongoing infection(s) that may affect brain function (e.g., HIV, syphilis, neuroborreliosis, or viral or bacterial meningitis/encephalitis), or history of infections that resulted in neurologic sequelae.		☐	☐
EXC#7 Any history of primary psychiatric diagnosis that the investigator considers may interfere with study assessments (e.g., schizophrenia, schizoaffective disorder, major depression, or bipolar disorder). • A history of major depression is not exclusionary in a participant if the participant is in remission with a Geriatric Depression Scale (15-item, short form) score ≤8.		☐	☐
EXC#8 Participant has a "yes" answer to C-SSRS suicidal ideation Type 4 or 5, suicidal behavior or has been assessed to be at risk of suicide, in the opinion of the investigator within 6 months before Screening, at Screening, or at the Baseline Visit, or has been hospitalized or treated for suicidal behavior in the past 2 years before Screening.		☐	☐
EXC#9 Participant has history of alcohol and/or moderate to severe substance use disorder (according to the DSM, 5th Edition) within the past 2 years. • Nicotine use is not exclusionary.		☐	☐

Medical Conditions – Imaging-related **EXC#10** MRI evidence based on central read of: a. >3 lacunar infarcts. b. Stroke involving a major vascular territory, severe small vessel, or white matter disease. c. Any territorial/cortical/other infarct >1 cm^3. d. White matter hyperintense lesions on the FLAIR sequence that correspond to an overall Fazekas score of 3 (Fazekas, 1987). e. >4 microhemorrhages. f. Any areas of superficial (leptomeningeal) hemosiderosis. g. A single macrohemorrhage >10 mm at greatest diameter. h. Vasogenic edema. i. Cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions. j. Space occupying lesions or brain tumors. k. Significant cerebral vascular pathology. l. Hydrocephalus/normal pressure hydrocephalus. m. Other MRI findings contraindicating participation in the study such assubarachnoid hemorrhage.		☐	☐
EXC#11 Participant is unable to tolerate MRI procedures (e.g., due to anxiety or claustrophobia) or has a contraindication to MRI, including but not limited to the presence of pacemakers that are not MRI compatible, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that would pose a potential hazard in combination with MRI. Those who are able to tolerate MRI with intermittent use of sedative medication as per local practice do not need to be excluded.		☐	☐
Medical Conditions – Cardiovascular-related **EXC#12** Uncontrolled hypertension at screening (i.e., average of 3 measurements of supine diastolic BP >95 mmHg or systolic BP >150 mmHg). Blood pressure measurements exceeding these limits may be repeated as warranted by the investigator, but values must be within the specified limits for the participant to be eligible for the study.		☐	☐
EXC#13 Known family or personal history of congenital long QT syndrome, symptoms of long QT syndrome, or risk factors for torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia, hypomagnesemia, or unexplained syncope.		☐	☐
EXC#14 Has an ECG at baseline that meets 1 of the following exclusionary conditions from an average of the 3 readings from triplicate 12-lead ECG: a. if QRS interval is <120 ms, then a QTcF ≥460 ms is exclusionary b. if QRS interval is ≥120 ms, then a QTcF ≥480 ms is exclusionary		☐	☐
EXC#15 Presence of an abnormal ECG that is clinically significant, including atrial fibrillation, complete left bundle branch block, second- or third-degree atrioventricular block, or evidence of acute or subacute myocardial infarction or ischemia.		☐	☐
EXC#16 Presence of any cardiac arrythmias that are not stable/ adequately controlled and/or any arrythmias associated with structural heart disease.		☐	☐
EXC#17 NYHA Class III or IV heart failure.		☐	☐
Medical Conditions – Hepatic/renal-related **EXC#18** Participants who have known, pre-existing, clinically significant renal impairment per investigator assessment.		☐	☐

EXC#19 Liver disease or liver chemistry values: a. ALT >2xULN. b. Total bilirubin >1.5xULN. Participants with Gilbert's syndrome can be included with total bilirubin >1.5xULN as long as direct bilirubin is ≤1.5xULN. c. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).		☐	☐
Medical Conditions – Infections and immune-related **EXC#20** Hepatitis B or Hepatitis C infection: a. Presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention. b. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention. **Note:** Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained. c. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. **Note:** Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.		☐	☐
EXC#21 Positive HIV antibody test.		☐	☐
EXC#22 History suggestive of exposure to, or past TB infection should undergo screening for TB disease at the discretion of the investigator, preferably with the interferon-gamma release assay. Participants who test positive should have further evaluation for active or latent TB disease prior to subsequent eligibility assessment. Participants with active or latent TB disease are not eligible for the study.		☐	☐
EXC#23 Any chronic active immune disorder requiring systemic immunosuppressive therapy within 6 months prior to Screening, including, but not limited to methotrexate, cyclosporin, azathioprine, and cyclophosphamide. The following exceptions apply: • Participants who are on continuous use of prednisone ≤10 mg/day or an equivalent corticosteroid only, with a stable regimen for at least 90 days prior to Screening, do not have to be excluded. • Participants who have intermittent short-term use (up to 21 days) of prednisone or an equivalent corticosteroid only, to treat an acute condition, do not have to be excluded.		☐	☐
Medical Conditions – Metabolic/endocrine-related **EXC#24** Screening serum vitamin B12 concentration <LLN or in the low normal range in the opinion of the investigator should be confirmed by serum homocysteine and serum methylmalonic acid assays. If either homocysteine or methylmalonic acid is >ULN per institutional standards, or if confirmation by homocysteine and methylmalonic acid is indicated but not available, then the participant will be excluded.		☐	☐
EXC#25 Folate <LLN or TSH >ULN at Screening.		☐	☐
EXC#26 Screening hemoglobin A1c >8% or poorly controlled diabetes (including frequent hypoglycemic episodes) during the last 12 weeks.		☐	☐

Medical Conditions – Other **EXC#27** History of cancer except any of the following: • If considered clinically cured. • If participant is not being actively treated with anticancer therapy or radiotherapy and is not likely to require treatment in the ensuing 3 years except for adjuvant hormonal therapy for localized breast cancer. • If documented remission of the cancer for at least 2 years. • Localized prostate cancer with no clinically significant progression within the past 2 years. • Localized basal cell carcinoma or squamous cell carcinoma of skin that has been excised with clear margins (i.e., melanoma with metastases would be excluded).		☐	☐
EXC#28 Any other medical conditions (e.g., cardiac, respiratory, gastrointestinal, or renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator(s) could affect the participant's safety or interfere with the study procedures.		☐	☐
EXC#29 Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins.		☐	☐
EXC#30 Planned surgery during the study which requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia, and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and participant safety.		☐	☐
EXC#38 Known genetic predisposition for clotting disorder or hemorrhagic disease.		☐	☐

Prior/concomitant therapy **EXC#31** The following rules on medications apply prior to study start or during the study, and participants whose medication regimens are not consistent with these rules will be excluded: a. If any of these medications (antipsychotics, opiates/opioids, cannabinoids, hypnotics, antidepressants, mood stabilizers, or stimulants) are used on a chronic basis, the treatment has to have been at a stable dose for at least 4 weeks before screening and should remain stable during the study. • In addition, if cannabinoids are used, they need to meet all of the following criteria: supplied by medical dispensary and permitted by local laws, used for medical reasons as instructed by the participant's physician. b. Any biologic drugs (including immunoglobulins, monoclonal antibodies, or other biologic drugs) with systemic exposure, and intraocular anti-VEGF therapies, whether investigational or approved, used within 6 months before screening. c. Any disease modification drug for AD, such as aducanumab and lecanemab, whether investigational or approved, used within 6 months before screening. All such participants not excluded under this criterion are still required to show amyloid positivity at screening. d. Vaccines for treatment of AD or other neurological diseases (except for infectious diseases) are prohibited within 1 year before screening and during the study. e. Routinely recommended approved vaccinations are allowed, as well as any vaccine against SARS-CoV-2 (COVID-19; including booster vaccinations; either approved or administered under an Emergency Use Authorization). If these vaccinations are due before the treatment period, they should be administered at least 7 days prior to Day 1. If these vaccinations are required during the treatment period, they should be administered at least 7 days before or 7 days after administration of the study intervention. f. Any investigational treatment within 5 half-lives or 90 days before screening, whichever is longer, and during the study. g. Anticoagulation medications within 90 days of screening and during the study, with the following exception: • Antiplatelet treatments (e.g., aspirin, clopidogrel, dipyridamole) are permitted (see exclusion criterion #34 for details regarding participants undergoing LP). h. Systemic immunosuppressive therapy within 6 months before screening and during the study, with the following exceptions: • Continuous use of prednisone ≤10 mg/day or an equivalent corticosteroid is allowed if treated with a stable regimen for at least 90 days prior to screening. • Intermittent short-term use of prednisone ≤30 mg/day or an equivalent corticosteroid is allowed as required for a maximum of 21 days to treat an acute condition.		☐	☐
Diagnostic assessments **EXC#32** Clinically significant abnormal blood or urine results at screening that may interfere with study procedures or participant safety or require further investigations or treatment.		☐	☐
EXC#33 Impaired coagulation (INR >1.5 × ULN at screening) or platelet count <50,000/μL.		☐	☐

Other exclusion criteria **EXC#34** Contraindication for LP includes deformity of the lumbosacral region of the spine that, in the investigator's opinion, contraindicates LP and taking anticoagulants (e.g., warfarin, direct thrombin inhibitors) or dual antiplatelet therapy. • LP that requires a guidance method that requires radiation, such as CT- or fluoroscopy-guided LP, is not permitted in the study; LP using a guidance method that does not require radiation, such as ultrasound, is permitted. Any participants who require a guidance method that requires radiation for LP for whatever reason will need to have an amyloid PET scan for eligibility purposes at the screening phase (unless they have acceptable historical amyloid PET or historical CSF amyloid reports) and will not participate in the CSF sub-study. • Participants who cannot undertake LP to collect CSF and who are not able to have amyloid PET at screening will be excluded. • Participants who cannot undertake LP are excluded from the CSF sub-study. Otherwise, inability to have an LP is not an exclusion criterion.		☐	☐
EXC#35 The participant resides in a skilled nursing facility, convalescent home, or long-term care facility. Participants enrolled in the study who subsequently require residence in these facilities during the study may continue in the study if considered suitable by the investigator and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirements.		☐	☐
EXC#36 If at screening, a participant with comorbidities that are likely to require non-study related medical procedures with additional radiation exposure is identified, the investigator must discuss with the medical monitor to determine if the total radiation exposure would be deemed to exceed maximum radioactive exposure allowed by country-specific regulations or 40 mSv for the study (whichever is the lower value). If the expected total radioactive exposure will exceed the limits defined above, then the participant will be excluded from participation in the PET sub-studies.		☐	☐
EXC#37 Any other issue which, in the opinion of the investigator, would compromise participant safety or the integrity of the study data.		☐	☐