Participant Informed Consent and Authorization Form

STUDY TITLE:	**Phase II Trial to Evaluate Safety and Efficacy of GM-CSF/Sargramostim in Alzheimer's Disease (SESAD)**
PROTOCOL NUMBER:	**COMIRB #19-2727**
FDA IND:	**152023**
STUDY DRUG:	**Sargramostim (also referred to as "study drug")**
SPONSOR/PRINCIPAL INVESTIGATOR:	**Huntington Potter, PhD** **University of Colorado** **Alzheimer's and Cognition Center** **Mail Stop 8680** **12700 E. 19th Ave.** **Aurora, CO 80045**
STUDY SITE INFORMATION:	**University of Colorado** **Anschutz Medical Campus** **Aurora, CO 80045**

Alzheimer's and Cognition Center
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Key Information:

Please read all of the information below and ask questions about anything you do not understand before deciding if you want to take part.

You are being asked to be in a research study. Participation in research is voluntary.
Some people in this study may have a medical condition or a disability that does not allow them to make important decisions for themselves. If you have been asked to decide for someone else whether they should be in this study, please read this consent form carefully. In this form, we use the words "you" and "your." If you are reading this form and deciding for someone else, the words 'you' and 'your' refer to that other person, not to you.

Purpose of this study: To learn more about the safety and effectiveness of a drug called sargramostim for improving cognitive function and memory in people with Alzheimer's disease. Sargramostim is an investigational drug, meaning it has not been approved by the FDA to treat Alzheimer's.

Procedures: If you agree to participate, the following will happen:

- You have already completed the initial step to determine eligibility by answering questionnaires and optionally, per the judgement of the study doctor, having a blood draw to test the level of beta amyloid OR pTau, both biomarkers of Alzheimer's disease, in your blood.
- Going forward, you will participate in a screening period of up to 12 weeks involving 3-4 visits to determine if you are eligible to then participate in the treatment period of the study. The screening period involves the collection of medical history, physical and neurological exams, blood draws, MRI, either a confirmatory lumbar puncture **or** a confirmatory PET scan, ECG and an optional lumbar puncture or PET scan. The treatment period lasts for 24 weeks and involves physical and neurological exams, blood draws, cognitive tests, PET/CT scans, injections of study drug (at clinic and self-administered at home), ECGs, MRIs, and a lumbar puncture **or** a PET scan.
- You will be assigned to one of two arms of the study: 1) receives study medication; 2) receives placebo. You do not get to choose which arm you are in nor will you be told which study treatment you are receiving. You must have a designated study partner throughout the study.
- Study participation last up to 10-1/2 months with up to 55 visits.

Risks: Participation in this study involves risks, including the following:

- Radiation exposure, pain from blood draws/IV insertion/lumbar puncture, edema or bleeding in brain from Amyloid PET, allergic reaction, fatigue, lack of energy, rash, itching, vomiting, diarrhea, abdominal pain, sore throat, chills, bone and joint pains, weight loss or gain, elevations in kidney or liver enzymes, fluid retention, injection site irritation, insomnia, headaches, passing fevers, bleeding into eye, shortness of breath, blood clots capillary leak syndrome, elevated blood pressure, potential strokes, heart failure, lung problems, occasional heart rhythm changes, altered stools, changes in tumor growth if you have a malignant tumor and "first dose effect" which might include elevation in heart rate, skin flushing, low blood pressure and lightheadedness. There is also potentially a risk of low white blood cell count or low absolute neutrophil count (a type of white blood cell) that might increase the risk of an infection. There is also the possibility of infection independent of low neutrophil count, which could range from mild to life-threatening.

Benefits: There is no guarantee that your health will improve if you join this study. This study may lead to information that could help patients and health care providers in the future.

Alternatives: Please discuss standard treatment and care options with your doctor.

Detailed Consent

WHAT IS THE PURPOSE OF THE STUDY?

Alzheimer's disease is a major medical problem in the elderly, affecting 12% of those over age 65 and 40-50% of those over age 85. Current treatments offer minor benefits in slowing the development of memory problems but do not stop or reverse the damage from the disease.

The purpose of this study is to determine if injections of a medicine called sargramostim in people with Alzheimer's disease is are safe and effective in improving cognitive function and memory and to evaluate its safety (side effects). Sargramostim has not been FDA approved as a safe or effective treatment for people with Alzheimer's Disease. That is why sargramostim will be referred to as a "study drug" or "study medication" throughout this document. This study is also being performed to find out more about how sargramostim works within the body over a longer time period than

previously studied. You are being asked to be in this research study because you have been diagnosed with mild-to-moderate Alzheimer's disease and are between the ages of 60 and 85 years, inclusive.

Participants in this study will be required to have a study partner participate with them. This study will have 2 different groups of research participants like you. One group will receive the study medication (sargramostim), and one group will receive the placebo. A placebo is a pill or a liquid that looks like medicine but is not real. It will have no medical effects on the person that receives it. Each research participant will be assigned to one of the groups randomly using a method of chance. This method is like rolling dice. You will not know if you have been assigned to the group receiving the study drug or to the group receiving the placebo. The study doctors and coordinators will not know if you are receiving the study drug or the placebo either. You will have a 2:1 chance of receiving the study drug over the placebo. This information needs to be kept secret so that the study is based on scientific results, not based on peoples' opinions. This method of conducting a study is called "double-blind" because neither the participants nor the scientists know which participants are in which group. However, study staff can give this information out if you have an emergency. If you are in an emergency, make sure you tell the emergency staff about this study. The emergency staff can contact the study team to review all relevant information. In the rest of this form, the term "study drug" refers to both sargramostim and placebo.

OTHER PEOPLE IN THIS STUDY
Up to 300 people (including participants and their study partners) from your area may be invited to participate in the study.

WHAT HAPPENS IF I JOIN THIS STUDY?
If you agree to join the study, after signing this Participant Informed Consent and Authorization Form, you will undergo a series of screening procedures to ensure you are healthy and safe to participate in the study during the screening period. This screening period can last up to 12 weeks.

If determined to be healthy, safe and eligible to participate in the study you will then enter the treatment period of the study. The treatment period would last for 24 weeks (6 months) and each week you will receive study drug (i.e., sargramostim or placebo) injection 7 days per week (Sunday-Saturday). Depending on your physical characteristics, such as height and weight, the daily dose may need to be given in 2 injections. You will come to the clinical research center for 4 visits during the treatment period and have an at-home weekly visit by a trained nurse 20 times,
to receive a dose of the study drug or placebo, have safety bloodwork collected, and review other health information. For the weeks when you have in-person visits to the clinical research center to receive your injections and have monitoring the remaining 6 daily injections will be administered at home. During the treatment period, you will have an at-home [weekly] visit by a trained home nurse 20 times. During the at-home visits, the trained home nurse will oversee study drug administration by the study partner until Week 3 and as needed thereafter, have safety bloodwork collected, and review other health information. Additionally, each week you will need to have a second blood draw to monitor safety labs, which can be collected at the clinical research center or at your local Lab Corp office.

Throughout your participation, the study team will be monitoring your health and well-being through review of adverse events, laboratory results, and examinations performed during the trial. For your safety, you may be asked during the study to stop treatment, or you may receive new replacement

syringes. While the study team will continuously monitor your lab results, you may not be told your specific results.

The estimated number of study visits for you, if you qualify, is 55, including:

- 4 screening visits (Tier 0.5-3) (with Tier 1-3 at clinical research center).
- **Optional** Tier 4 screening visit for either a lumbar puncture or amyloid PET scan (at clinical research center, depending on which test you chose for entry criteria)
- 24 treatment period visits (4 clinical research center visits approximately 6 weeks apart, and 20 at home visits with a home nurse)
- 24 additional weekly blood draw visits
- 1 End of Treatment visit (at clinical research center)
- 1 End of Treatment lumbar puncture and blood draw visit (at clinical research center if you chose the lumbar puncture for entry, or if you chose to enroll in the **optional** lumbar puncture substudy)
- 1 end of study FDG PET visit (at clinical research center).
- 1 visit in the post-treatment follow-up phase (at clinical research center).
- If you chose to have an amyloid PET scan for entry to the study, or if you chose to participate in the optional amyloid PET substudy, you would have an additional Amyloid PET scan during follow-up phase

The study drug must be kept within a specific temperature range at home, and the study will be providing a small case to keep the medication in within your home refrigerator, as well as a temperature logging device to be kept with the drug. The study medication will be delivered weekly to your home during weeks when there are at-home visits by the home nurse.

Your decision to be in the study is voluntary. You can stop being in the study at any time, without penalty. If you leave the study, your study partner's role will also stop. You may have to leave the study early even if you want to stay in the study. This could happen if:

- The study doctor or sponsor thinks it is in your best interest to leave the study
- You do not follow study instructions
- Your study partner does not follow the instructions of the study doctor and an acceptable study partner replacement cannot be found
- There is a change in your medical condition
- The study is stopped by the sponsor, the Institutional Review Board (IRB) or any regulatory authority (for example, the FDA) for any reason

If you want to leave the study early for any reason, please tell the study doctor or study staff. You will not have to give a reason for leaving the study early. If you leave the study, the study doctor and study staff will still be able to use your information that they have already collected.

Detailed descriptions of the study visits and activities follow.

SCREENING

After the initial blood test and questionnaire, the rest of the screening will be conducted over 3-4 visits within a 12-week timeframe.

FIRST FULL SCREENING (TIER 1)

At the Tier 1 screening visit we will review with you in greater detail the reasons for the study, the nature of the study treatment and the study procedures, the number of visits involved, as well as the risks and the possible benefits of your participation. You will have an opportunity to read this Participant Informed Consent and Authorization Form and have your questions answered after which you can either sign this form, or you can decide not to participate in the study. If you are a female who is capable of getting pregnant, a urine pregnancy test will be performed. A urine sample will be collected to test for non-prescription drugs and cannabinoids in all participants.

Once you have signed this form, we will administer a short test of memory and cognition.

Depending on your result, you may or may not qualify to continue with the screening process of this study. If you do qualify, we will proceed with the screening process. This includes:

- Recording your medical history
- Recording your medications
- Vital signs including blood pressure, pulse, height, and weight
- Heart tracing (ECG)
- Physical and neurological exam.
- Drawing about one tablespoon of your blood to determine your blood count and the health of your liver and kidneys
- Assessments of mood.

If you meet the study criteria from this visit for screening, you will continue on to the second full screening visit procedure.

SECOND FULL SCREENING VISIT (TIER 2)
At the second full screening visit, the following procedure will happen:

- Brain scan (MRI) to ensure that there are no additional risks to your participation. If deemed necessary to complete the procedure, a study physician may prescribe lorazepam to ease symptoms of claustrophobia that some individuals might experience, the cost of which will be reimbursed by the study.

If you qualify based upon the MRI, you will progress to the third full screening visit procedures.

THIRD FULL SCREENING VISIT (TIER 3)
For the third full screening visit, you have the choice to have elevated amyloid confirmed either by lumbar puncture OR by Amyloid PET scan. You will indicate this choice later in this form.

The following procedures will happen:

If you chose to have the confirmation of elevated amyloid done via lumbar puncture:

- Blood draw.
- Lumbar puncture (also known as a spinal tap) to obtain cerebrospinal fluid for analysis to determine the level of amyloid and tau proteins in your brain. This fluid surrounds your brain and spine, and then is contained in a sack of fluid for several inches below where the spinal cord ends. During a lumbar puncture, a small needle is inserted between the bones of the spine in your lower back into this sack of fluid, and a small amount of spinal fluid (about 15 mL or a little less than a tablespoon) is removed.

If you qualify for the study based upon the lumbar puncture and all other screening visits, you will be eligible to continue with the study treatment period.

If you choose to have the confirmation of elevated amyloid done via Amyloid PET scan:

- Screening Positron Emission Tomography (PET) scan to measure the amount of amyloid in the brain. Amyloid is a protein found in the brain of patients with Alzheimer's disease.

There is an **optional substudy that, if you choose to participate, will take place during the screening period. If you choose to confirm elevated amyloid via the lumbar puncture, you may choose a Screening Amyloid PET scan substudy. The purpose of this scan is to measure the amount of amyloid in the brain. Amyloid is a protein found in the brains of patients with Alzheimer's disease. If you do not wish to take part in this OPTIONAL testing, you can still participate in the study. A separate Informed Consent Form has more detail regarding this procedure.

If you choose to confirm elevated amyloid via the Amyloid PET scan, you may choose a Lumbar Puncture substudy. The purpose of this substudy is to obtain cerebrospinal fluid to measure proteins such as amyloid in the brain, as well as to look at a variety of other markers of neuronal health. If you do not wish to take part in this OPTIONAL testing, you can still participate in the study. A separate Informed Consent Form has more detail regarding this procedure.

TREATMENT PERIOD

Below is a table that outlines what will be done at each visit.

	WEEK of Visit																									
Visits	**Baseline**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**EOT**	**F/U**
Tolerance Interval for Visit (days)	0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+2-10	+/-7
Concomitant Med Review	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
Physical / Neuro Exam	X											X													X	X
Study Drug Injection Training	X																									
Study Medication Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Assessment of Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cognitive Assessments	X											X													X	X
Safety Assessments																										
Safety Assessment Questionnaires	X											X													X	X
Asking about Possible Adverse Events	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
Injection Site Review	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	
Vital Signs	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
Serum Anti-Drug Antibody (ADA)	X					X						X						X							X	X
Safety Blood Draws	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
Enhanced Safety Blood Draws	X					X						X						X							X	
ECG												X													X	
MRI						X						X						X							X	X
Additional Assessments																										
Lumbar Puncture (Spinal Tap (if chosen for entry or optional substudy)																									X	
Blood Draw (biomarker and assay)	X																								X	X
FDG PET	X																								X	
Amyloid PET (if chosen for entry or optional substudy)																										X

BASELINE VISIT

This clinical research center visit will take place approximately 12 weeks after the initial screening visit. The following things will be done at this visit:

- Vital signs including blood pressure, pulse and weight
- Physical and neurological exam
- Blood draws of about three tablespoons of your blood to determine your blood count and the health of your liver and kidneys, and to measure proteins (biomarkers) that are associated with Alzheimer's disease
- Several tests of your memory and thinking skills and assessments on how you are feeling emotionally and functioning in your daily life.
- Training by a study nurse or clinician on how to inject the drug at home.
- Remaining six doses for at-home administration will be dispensed to you.
- Baseline FDG-PET scan
    - The Baseline FDG-PET scan: If you meet all criteria and choose to join the study, we will need to perform an FDG-PET scan of your brain at the study's beginning. We will ask you to arrive for your PET scan at the CU Anschutz Research Imaging Center in the morning hours after an 4 hour fast. Once you arrive at the imaging center, you will rest quietly for about 30-45 minutes. A small blood sample will be taken via a finger prick to check your blood sugar levels. After verification of normal blood sugar levels, a small amount of a radioactive glucose tracer, 18F-Fluorodeoxyglucose, will be injected into your blood stream through a small needle inserted into a vein on your arm. You will again rest quietly for about 45 minutes. You will then undergo a Positron Emission Tomography (PET)/ Computed Tomography (CT) scan of your head and neck. The scan will last approximately 20-30 minutes.
- The study nurse or clinician will observe you or your study partner inject the first dose of study drug under the skin after training.

WEEKS 1-24 BLOOD DRAW VISITS

In addition to the weekly in-clinical research center visits/at home nurse visits that occur, you will be required to have an additional weekly blood draw that will occur either at a contracted central laboratory site or at the University of Colorado Anschutz Medical Campus. The choice of location is up to you. At these visits, the following procedure will take place:

- Blood draws to evaluate the numbers of certain cells in your blood.

WEEKS 2-5, 7-11, 13-17, and 19-24 AT HOME VISITS

During the at home nurse visits, the following procedures will take place:

- Inject the study drug
- Check vital signs
- Check your injection site
- Ask about any changes to your health or medications or any reactions you have had to the drug.
- Check compliance of at-home injections.
- Blood draws to determine your blood count and the health of your liver and kidneys

On one day of each of these weeks, the study drug will be transported to your home by delegated study staff so that it is re-supplied for your at-home injections the following week.

ADDITIONAL PROCEDURES AT SPECIFIC VISITS

At these visits, which will occur at the research center, the following procedures will take place:

- During the Week 6, 12, 18 and End of Treatment (EOT) visits, you will also undergo a brain scan (MRI). If deemed necessary to complete the procedure, a study physician may prescribe lorazepam to ease symptoms of claustrophobia that some individuals might experience, the cost of which will be reimbursed by the study.
- During week 12 and EOT visits, you will have a physical and neurological exam, tests of memory and thinking skills and assessments on how you are feeling emotionally and functioning in your daily life, and Heart tracing (ECG).
- At the EOT visit, you will have an FDG-PET scan and a lumbar puncture (if you chose the lumbar puncture for screening or if you chose to participate in the optional lumbar puncture substudy), like the tests done during screening
- During the week of the EOT visit, you will have safety blood draws at approximately 2 days and 9 days after stopping study drug.

FOLLOW-UP IN-CENTER VISIT

Around 45 days after you are done taking study drug, you will return to the clinic. The following things will be done at this visit:

- Check vital signs
- Ask about any changes to your health or medications
- Physical and neurological exam
- Several tests of your memory and thinking skills and assessments on how you are feeling emotionally and functioning in your daily life.
- Brain scan (MRI). If deemed necessary to complete the procedure, a study physician may prescribe lorazepam to ease symptoms of claustrophobia that some individuals might experience, the cost of which will be reimbursed by the study.
- Blood draw to determine your blood count and the health of your liver and kidneys, and to measure proteins (biomarkers) that are associated with Alzheimer's disease.
- Amyloid PET scan like the one during screening (if you chose the Amyloid PET scan for screening or if you chose to participate in the optional Amyloid PET scan substudy).
- Note: Additional safety monitoring may occur post study completion if clinically significant abnormal results occur.

INTERRUPTION OF TREATMENT

At the discretion of the Principal Investigator, you may request an interruption of treatment due to commitments such as travel obligations. The interruption is permissible for one block of time, up to 4 weeks in duration (i.e., 28 dosage days). The time taken off treatment will be added to the end of the treatment period to complete 24 total weeks of treatment.

Optional Consent and Authorization for Data (including imaging results) and Biological Samples (Blood and Cerebrospinal Fluid (CSF)) Banking for Future Research

The study doctors would like to keep some of the data and biological samples (i.e., blood and CSF samples) that are taken during the study but are not used for other tests. If you agree, these data and biological samples will be kept and may be used in future research to learn more about Alzheimer's

disease. The research that is done with your data and biological samples is not designed to specifically help you. It might help people who have Alzheimer's disease and other diseases in the future. Reports about research done with your data and biological samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and biological samples will not affect your care.

The choice to let the study doctors keep the data and blood samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. Even if you decide now that your data and biological samples can be kept for research, you can change your mind at any time and contact your study doctor to let them know that you do not want the study doctors to use your data and biological samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until the study doctors decide to destroy them.

If your data and biological samples are given to other researchers in the future, the study doctors will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and biological samples are used for genetic research (about diseases that are passed on in families). Even if your data and biological samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and biological samples will only be used for research and will not be sold. The research done with your data and biological samples may help to develop new products in the future, but there is no plan for you to be paid.

We may share data from our research with other researchers or data banks. One such data bank is called dbGAP, which collects genetic and other data and is sponsored by the National Institutes of Health. By broadly sharing data in data banks like this, we can make our discoveries more accessible to other researchers. Information that directly identifies you will not be sent to these data banks.

Because your genetic information is unique to you, there is a small risk that someone could connect the information back to you. Also, genetic research and broadly sharing data may involve risks to you or people like yourself that are unknown at this time

The possible benefits of research from your data and biological samples include learning more about what causes Alzheimer's disease and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. The study doctors will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or biological sample collection and storage by the study doctors.

Please read each sentence below and think about your choice. If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and biological samples, you may still take part in the study, and you may change your decision later.

1. I give my permissions for my data and biological samples to be kept by Dr. Huntington Potter for use in future research

☐ Yes ☐ No _____Participant Initials _____LAR/ Initials (if needed)

2. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.

   ☐ Yes ☐ No _____Participant Initials _____LAR/ Initials (if needed)

WHAT ARE THE POSSIBLE DISCOMFORTS OR RISKS?

Answering the study doctor or study staff's questions could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while answering questions. You have the right to refuse to answer any questions.

Possible side effects of the study drug: sargramostim

You may have problems because of the drug used in this study. These problems are called side effects. Some side effects are just a bother and others could harm you. There may be some side effects that we do not know about yet. The research might involve risks to you that are currently unforeseeable.

There is always a chance that any medical treatment may cause you some discomfort or harm and the drugs or procedures in this study are no different. There may be other risks or side effects that occur that we do not know about at this time. It is important for you to tell us when you experience such a side effect. The study team follows guidelines to minimize risks to participants.

The following side effects occur more frequently in patients taking sargramostim as compared to those taking placebo:

Common but non-life-threatening side effects include:

- "First dose effect," which might include elevation in heart rate, skin flushing, low blood pressure, and lightheadedness
- Fatigue
- Lack of energy
- Rash
- Itching
- Vomiting
- Diarrhea
- Abdominal pain
- Sore throat
- Chills
- Bone pains
- Joint pains
- Weight loss or gain
- Elevations in kidney or liver enzymes have been reported
- Fluid retention
- Injection site irritation
- Insomnia
- Headaches

- Passing fevers

Less common but potentially serious side effects include:

- Bleeding into the eye
- Allergic reactions to the study drug (indicated by rashes or shortness of breath)
- Excessive increase in white blood cell count. This could lead to:
  - Extreme bone pain
  - Blood clots
  - Capillary leak syndrome
  - Elevated blood pressure
  - Potential strokes
  - Heart failure
  - Lung problems
  - Fluid retention in the lung lining and in the heart lining
- Shortness of breath
- Occasional heart rhythm changes (supraventricular tachycardia)
- Black, tarry, or bloody stools
- Throw up that looks like coffee grounds
- In case of a malignant tumor, sargramostim might act as a growth factor

Potential side effects of unknown frequency, which may increase the risk of infection:

- Low white blood cell count (leukopenia)
- Low neutrophil count (neutropenia)
- Risk of infection, ranging from mild to life threatening

Possible risks of Amyloid Related Imaging Abnormality (ARIA):

ARIA has been identified as an event that may occur following treatment with certain drugs that specifically target amyloid in the brain. There is no evidence that sargramostim causes or increases risk of ARIA. However, there is a risk that an ARIA event may take place following removal of amyloid from the brain. ARIA events are identified and monitored using Magnetic Resonance Imaging (MRI).

ARIA events can be classified into two main categories:

- (ARIA-E) - Amyloid Related Imaging Abnormality due to edema or swelling in the brain
- (ARIA-H) - Amyloid Related Imaging Abnormality due to microhemorrhages, which are small areas of bleeding in the brain

Possible risks associated with lumbar puncture (LP):

- These might include pain, bleeding, infection and headache. To limit discomfort, the skin, surrounding tissue and underlying muscle will be numbed with a drug called lidocaine. This is similar to anesthesia delivered during a dental procedure, such as a tooth extraction. Lidocaine administration may cause a brief burning sensation. During the LP you may also experience brief pain lasting seconds in the lower back during insertion of the needle. Rarely, this sensation or some numbness in the leg may persist for days. Less than 1 in 100 patients are allergic to the iodine solution used to clean their back and will develop a rash. After an LP, 5 to 15 out of 100 individuals develop a headache that is worse when standing and disappears when lying down. If it occurs, this headache typically begins 6-48 hours after the LP, and may last from 1 to 6 days. Lying flat and taking caffeine sodium benzoate can help treat the headache. If it persists despite this treatment, there are additional procedures a physician can

do to help resolve the headache. To reduce the likelihood of a temporary headache after the LP, you will be asked to lie on your back for 2 to 3 hours after the procedure. Post-LP headache may be treated with oral hydration, analgesics such as acetaminophen or ibuprofen, and caffeine. If the headache persists for more than 7 days, an epidural blood patch may be advised for relief. This procedure can be performed by any anesthesiologist, but the cost of this procedure would be the responsibility of you or your insurance. About 3 in 100 individuals with post-LP headache also develop double vision that can last a few days to a few weeks. Approximately 3 in 100 individuals will develop transient hearing problems or ringing in the ears lasting a few days. Infection may occur at or near the LP site, although this is rare and precautions are taken throughout the procedure to reduce this possibility.

- Because of the risk of temporary visual blurring or headache, you should arrange for transportation after the procedure in case you are temporarily unable to drive.

Possible risks of having a Magnetic Resonance Imaging (MRI) procedure:
In this study we will take Magnetic Resonance Images (MRIs) of your head. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working.

You should NOT have an MRI if you have certain metals or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces.

The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

If you are pregnant, be sure to tell the person giving you the MRI.

Possible risk of using (optional) lorazepam for MRI procedure
Lorazepam may cause drowsiness or unsteadiness. You should not operate heavy equipment or drive a car after taking the medication. You need to have a friend or family member drive you home after any research MRI appointment where lorazepam is used. There is a rare risk of paradoxical agitation and/or confusion that may occur in some individuals after taking lorazepam. You should not use alcohol 24 hours before or after taking lorazepam.

Possible risks of PET Procedures:
Possible discomforts or risks of an IV:
As mentioned above, an IV catheter will be temporarily placed in your arm or hand to inject the imaging agent. You will feel a brief sharp pain/discomfort when the needle used to place the IV catheter is placed through your skin. Sometimes the placement of an IV may cause redness, swelling or bruising at the site of the IV. This is temporary and should get better on its own. In very rare cases, placement of an IV could cause infection or a blood clot. During the injection of the imaging agent through the IV, you may feel a warm or tingling sensation at the site of the injection. The IV will be placed in the arm during the procedure.

Possible discomforts of a PET/CT scan:

You will be asked to lie down on the scanner bed for 20-30 minutes. Pillows, padding, and blankets can be provided for your comfort, but there may be some discomfort from lying down on the scanner bed. Some people may also feel claustrophobia (fear of being in tight places).

If you choose the Amyloid PET scan for Tier 3 screening:
If you choose to do an Amyloid PET scan for screening, we will perform an Amyloid PET scan of your head by using a radioactive tracer such as flutemetamol F18, also known as Vizamyl,. This tracer binds with the amyloid beta depositions within the brain. Vizamyl has been approved for research use in the United States for imaging amyloid plaques in the brains of people with Alzheimer's disease.

The Vizamyl radioactive tracer is estimated to give you a dose of 5.92 mSv, roughly equivalent to 1-2 years of natural background radiation dose. This is an estimate - the amount of radiation dose you receive could be higher or lower, depending on how much tracer is injected into your body, and your body size in relation to the dose. The radioactive drug is eliminated from the body quickly and should be gone from your body within 24 hours. Most of the drug will be eliminated through urination.

Other protocol-required PET scan:
As part of this study, we will perform an FDG PET scan of your head by using a radioactive tracer. We will first inject the tracer. Then we will look at the head through a scanner. The radioactive tracer is estimated to give you a dose of 6.3 mSv, roughly equivalent to 1.5 year's natural background radiation dose. This is an estimate - the amount of radiation dose you receive could be higher or lower, depending on how much tracer is injected into your body, and your body size in relation to the dose. The radioactive drug is eliminated from the body quickly, and should be gone from your body within 24 hours. Most of the drug will be eliminated through urination.

As part of the Amyloid PET and FDG PET, we will also perform a CT scan (Computed Tomography) of your head. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation. The instrument produces cross-sectional images of the body including the head. Using the CT information combined with the PET radiotracer, we are able to construct 3-dimensional images of your brain allowing for this research to be conducted. The CT scan for this particular study has been estimated to be 0.6 mSv. Total estimated radiation dose for the combined Amyloid PET/CT imaging is 6.5 mSv and for the FDG-PET/CT imaging is 7 mSv. This dose is well below the research participant single dose limit of 30 mSv and annual dose limit of 50 mSv.

Although not everyone is exposed to radiation from medical imaging scans, everyone is exposed to natural background radiation. There is natural background radiation in the soil, in water that we drink, in vegetables that we eat, in the air, from the sun, and within small amounts of radioactive atoms in our own bodies. However, increased radiation sources are associated with some increased risk of cancer over a person's lifetime.

If you would like more information regarding radiation, please ask the study coordinator or investigator for a copy of "The University of Colorado Radiology Adult Dose-Risk Smartcard."

Please inform your doctor if you have had any radiation exposure in the past year, from research studies or standard clinical procedures. This is suggested to limit your radiation exposure and minimize risk. Radiation exposure includes x-rays, cardiac catheterization, fluoroscopy, as well as any scans that included the injection of radioactive materials.

Possible risks of having blood drawn

In this study we will need to get blood from you as described in the "What Happens if I Join this Study" section of this form. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Possible risks of multiple study drug injections

Common side effects include bruising, swelling and pain at the site of the needle insertion.

It is rare, but an infection can occur at the site of the needle insertion. One of the study nurses will examine and monitor the injection sites during the in-clinical research center study visits.

Other:

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus that are currently unclear.

The study may include risks that are unknown at this time.

Tier 3 Screening Option

Please choose which procedure you would prefer to confirm elevated amyloid, which is required as part of the Tier 3 screening:

☐ Amyloid PET Scan _____Participant Initials _____LAR/ Initials (if needed)

☐ Lumbar Puncture _____Participant Initials _____LAR/ Initials (if needed)

WHAT ARE THE POSSIBLE BENEFITS OF THE STUDY?

This study is designed for the researcher to learn more about the effect of the study drug on Alzheimer's disease. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

ARE THERE ALTERNATIVE TREATMENTS?

There may be other ways of treating your Alzheimer's disease. These other ways include medications such as donepezil, rivastigmine, galantamine, memantine, lecanemab, or donanemab. You may also choose to get no treatment at all.

You should talk to your doctor about your choices to be certain that you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other medications available to you. During this study, you may also take the Alzheimer's medications listed above, except for lecanemab and donanemab.

You should inform your doctor about previous participation in this study before beginning lecanemab or donanemab therapy.

WHO IS PAYING FOR THIS STUDY?
The study is being paid for by the Alzheimer's Association, a National Institute of Health grant, and funds from the University of Colorado Alzheimer's and Cognition Center.

WILL I BE PAID FOR BEING IN THE STUDY?
To help defray your cost of participation for items such as travel costs, if randomized, you will receive a $75.00 payment at the end of the 24-week treatment period even if you cannot or choose not to complete the study, and you will receive a $25.00 payment after the follow up visits. Additionally, you will receive a $75.00 payment after each lumbar puncture, and a $125.00 payment after each amyloid PET procedure, for a total maximum of $500.00.

It is important to know that payments for participation in a study are taxable income.

FINANCIAL DISCLOSURE
Dr. Huntington Potter (the principal investigator on this study) is a co- inventor of certain methods evaluated in this study, which are owned by the University of South Florida. A plan to manage any potential conflict of interest has been approved by the University of Colorado. Dr. Potter has relinquished any and all personal rights to shared royalties from USF patents and has instructed the USF Technology Transfer Office to transfer any such income that might come in the future to the University of Colorado Foundation to support research by the Potter Alzheimer Dementia Fund. Please feel free to ask any additional questions that you may have about these matters.

WILL I HAVE TO PAY FOR ANYTHING?
It will not cost you anything to be in the study.

IS MY PARTICIPATION VOLUNTARY?
Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

CAN I BE REMOVED FROM THIS STUDY?
The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

WHAT HAPPENS IF I AM INJURED OR HURT DURING THE STUDY?
If you have an injury while you are in this study, you should call Dr. Huntington Potter 303-724-7385 immediately. If you consider an event to be an emergency, please call 911 for emergency services.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

WHO DO I CALL IF I HAVE QUESTIONS?

The researcher carrying out this study is Dr. Huntington Potter. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Huntington Potter at 303-724-7385. You will be given a copy of this form to keep.

You may have questions about your rights as a participant in this study. You can call the study doctors with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the trial and results. You can search this website at any time.

What happens to data collected in this study?

The data we collect will be used for this study but may also be important for future research. With your consent on this form, your data may be used for future research or distributed to other researchers for future study without additional consent if information that identifies you is removed from the data.

Certificate of Confidentiality

This study has been issued a Certificate of Confidentiality from the federal government to help protect your privacy. The Certificate prohibits the researchers from disclosing your name, or any identifiable information, documents or biospecimens from the research, with the exceptions listed below. A certificate provides protections against disclosing research information in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

These protections apply only to your research records. The protections do not apply to your medical records. The researchers may disclose your name or identifiable information, document or biospecimen, under the following circumstances:

- To those connected with the research,
- If required by Federal, State or local laws,
- If necessary for your medical treatment, with your consent,
- For other scientific research conducted in compliance with Federal regulations,
- To comply with mandated reporting, such as a possible threat to harm yourself or others, reports of child abuse, and required communicable disease reporting, or
- Under other circumstances with your consent.

A Certificate of Confidentiality does not protect information you or a member of your family voluntarily release.

WHO WILL SEE MY RESEARCH INFORMATION?

The University of Colorado Denver | Anschutz Medical Campus (the University) and its affiliated health systems have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the

consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include

- University of Colorado Denver | Anschutz Medical Campus
- University of Colorado Health

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not give us this permission, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information, but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Huntington Potter, Ph.D.
Kurt N. and Edith von Kaulla Memorial Professor of Neurology
Director, University of Colorado Alzheimer's and Cognition Center
Research Complex #2, Rm. 4010
Anschutz Medical Campus
University of Colorado, Denver MS 8608
12700 E. 19th Ave.
Aurora CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA), the National Institutes of Health, and the Office of Human Research Protections (OHRP) that protect research participants like you.
- The Institutional Review Board that is responsible for overseeing this research
- The study doctor and the rest of the study team.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research
- The Data Safety Monitoring Board (the committee that reviews the safety of the study).

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names and any other personally identifiable information of the research participants, like you, private.

You have the right to request access to your personal health information from the Principal Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study is completed.

The investigator (or staff acting on behalf of the Principal Investigator) will use your information for the research outlined in this consent form. They will also make *all or some* of the following health information about you collected in this study available to:

- Labcorp (for blood and urine testing)

INFORMATION ABOUT YOU THAT WILL BE SEEN, COLLECTED, USED AND DISCLOSED IN THIS STUDY:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to diagnosis(es), medical history and physical examination, laboratory or tissue studies, radiology studies, procedure results
- Research visit and research test records
- Psychological and mental health tests
- Alcoholism, alcohol or drug abuse

WHAT HAPPENS TO DATA (INCLUDING IMAGING DATA) AND BIOLOGICAL SAMPLES (INCLUDING BLOOD, CEREBROSPINAL FLUID) THAT ARE COLLECTED IN THIS STUDY?

Scientists at the University and the health systems involved in this study work to find the causes and cures of disease. The data and biological samples collected from you during this study are important to this study and to future research. If you join this study:

- The data and biological samples given by you to the investigators for this research no longer belong to you.
- The Sponsor or Investigator of this study may examine your data or biological samples collected during the study.
- If data or biological samples are in a form that identifies you, CU Anschutz or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA AUTHORIZATION FOR OPTIONAL ADDITIONAL STUDY PROCEDURES

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ (LAR)

OR

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

_____ (LAR)

AGREEMENT TO BE IN THIS STUDY AND USE MY DATA

I have read this paper about the study, or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use, and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I understand that I will get a signed and dated copy of this consent form.

PARTICIPANT

Signature:_____ Date:_____

Print Name:_____

Signature Line for Legally Authorized Representative and/or Proxy Decision Maker, if applicable

_____ Date:_____
Legally Authorized Representative/Proxy Decision Maker Signature

Print Name: _____

Participant Assent (if consenting via LAR/proxy):_____

Print Name: _____

Date: _____

Consent form explained by:_____ Date:_____

Print Name: _____