Informed Consent to Act as a Research Subject In:

A Safety and Pharmacokinetics-Pharmacodynamics Study in Subjects with Early Alzheimer's Disease

This consent form describes a research study and your role as a research subject. This document is intended to inform you about the possible risks and benefits of the research study, other options that may be available to you and your rights as a research subject. Please read this consent form carefully and do not hesitate to ask the study doctor any questions you may have about the study or the information provided below.

Your participation in this study is entirely voluntary. Please take as much time as you need to discuss the study with your doctors, family and friends. The decision to participate or not is yours. If you choose to participate, you have the right to withdraw from the study at any time.

A description of this research study will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

This study is being conducted by the Alzheimer's Disease Cooperative Study (ADCS), through a grant from the National Institute on Aging (NIA). Drug will be provided by QR, Inc.

Investigator(s)
Sample Doctor, MD
Sample Doctor, PhD

Location
Site Address
Site Address
Site Address
Site Address

Protocol Title
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamic (PD) Effects of Posiphen® in Subjects with Early Alzheimer's Disease (AD)

Protocol Number ADC-043-DISC

Why is this study being done?

Alzheimer's disease (AD) is a brain disease that results in a loss of mental function.

A protein called "amyloid" or "beta-amyloid" forms plaques in the brains of people with AD, and scientists believe the build-up of amyloid may play a key role in the developing the disease. The drugs currently approved by the United States Food and Drug Administration (FDA) for AD treat symptoms such as memory loss but do not prevent the disease, delay its onset or slow its progression.

As an alternative to being in the study, you may ask your doctor about receiving Aduhelm™ (an antibody also known as aducanumab) which has received accelerated approval by the FDA for the treatment of AD. This treatment Aduhelm™ is not permitted within this study.

You are being invited to take part in a research study that will look at an experimental drug called "Posiphen". This means it has not been approved by the United States Food and Drug Administration (FDA) for the treatment of AD. You are being asked to take part in this study because you are 55-89 years old (inclusive), in good health with no frailty, and have a clinical profile consistent with early AD including Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD) or Mild AD.

Posiphen is being developed as an anti-amyloid drug that may delay the onset or slow the progression of possible AD-related brain damage due to amyloid build-up.

The purpose of this study is to:

- test the safety and tolerability of the study drug.
- measure the amount of the study drug and drug-related material in the cerebrospinal fluid (CSF, the fluid surrounding the brain and spinal cord) and blood.
- measure the effect of Posiphen on the levels of certain proteins (biomarkers) associated with AD in the blood and CSF.

In this study, participants will be given either active study drug (Posiphen 60 mg taken either once, twice or three times per day) or placebo (capsules that looks like the study drug but do not contain any active drug).

How many people will take part in this study?

This study is being conducted at 3 to 6 sites across the US. If you are eligible and agree to participate, you will be one of approximately 24 individuals enrolled in this study.

What will happen if I take part in this research study?

In this study, participants will take one capsule of Posiphen or placebo, up to three times a day by mouth for up to 25 days.

This is a randomized, double-blind, placebo-controlled study. This means that if you choose to participate, it will be determined by chance (for example, flipping a coin) which of the two groups (active or placebo) you will be assigned to at each dose level (60 mg once per day, 60 mg twice per

day or 60 mg three times per day of active study drug, or placebo). Since approximately two-thirds of subjects will receive active study drug, there is a greater chance that you will receive Posiphen rather than the placebo.

Neither you nor the study personnel will know whether you are receiving the active study drug or placebo. However, if it becomes medically necessary, Dr. [INSERT PI NAME] may obtain this information.

Because this is a research study, Posiphen will be given only during this study and not after the study is over.

If you are to qualify and agree to participate in the study, your participation will last up to 68 days and will require 5 study visits - including an approximate 3-day stay (Confinement visit) at the clinical research unit. One of those 5 "visits" will be done over the telephone. Study staff will explain this to you and work out the best schedule for you to complete all of the study procedures.

To participate in this study, you must have a spouse, friend or relative (called a "Study Partner"), who is willing to:

- Attend the entire screening and baseline visits with you. Your study partner should also stay for the first three hours of the confinement visit and return to drive you home.
- Answer questions about your memory, behavior and daily functioning.
- Make sure that you are taking the study drug as instructed.
- Tell the study staff of any changes in your health status over the period of this study.

While you are in the study, you must:

- Follow the instructions you are given.
- Come to the study site for all visits.
- Tell the study staff about any changes in your health.
- Tell the study doctor about all medications you are taking and check with the study doctor before you begin taking a new medication.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

During this study, Dr. [INSERT PI NAME] and [his/her] staff will be monitoring your condition.

Description of Visit Activities

Screening Visit (Visit 1)

The first part of the study is called the Screening Period. During this time, the study team will decide if you qualify to be in the study. The screening activities could take place over 2 days at the clinic over a 6 week period. Each visit may take several hours to complete.

At the beginning of your first clinic visit, the study staff will explain all of the study procedures and answer any questions that you and your study partner may have.

You or your legally authorized representative (if applicable), and also your study partner must sign this consent form before beginning the screening process. After you sign consent to participate you should report all injuries, reactions to medications or illnesses to the staff at this site so that it can be recorded in your study records.

During the Screening Visit (which includes your Study Partner):

- Your general medical history will be recorded and your medical records will be reviewed.
- A list of the vitamins and current medications you are taking will be collected.
- Your weight and vital signs (blood pressure, pulse, temperature, and respiration rate) will be recorded.
- A physical and neurological exam will be performed.
- An electrocardiogram (ECG) will also be performed. An ECG is a tracing test that measures electrical signals from your heart.
- You will be given tests of your memory and thinking and you will be asked questions about your daily functioning and your behavior. You can skip any questions you do not want to answer, and you can take breaks if needed.
- Blood will be drawn from a vein in your arm and you will be asked for a urine sample. The blood and urine samples are for routine laboratory tests to make sure you do not have any medical conditions that would interfere with your participation in the study.

  You may undergo an MRI (magnetic resonance imaging) scan during the Screening Period if you have not had a scan within the last 12 months before the Screening Visit. An MRI uses a large magnet and computer equipment to produce electronic pictures of your brain. Each MRI will take approximately 45 minutes to complete. You will lie on your back and enter the MR machine for the scan, during which time you will hear loud knocking noises.

  People with pacemakers, aneurysm clips, cochlear implants, or metal/foreign objects in their eyes are not permitted to undergo MR studies.

- A lumbar puncture (LP) - also known as a “spinal tap” - will be performed. A lumbar puncture is a procedure that involves inserting a needle in the lower back in order to collect a small amount (16-20 mL - approximately 1 tablespoon), of the spinal fluid that surrounds the brain and spinal cord. Your body will replace this spinal fluid within 1-2 hours. If you have had a lumbar puncture for another study, within the last 90 days at this site, the samples may be used in place of the screening lumbar puncture.

  You will be asked to fast overnight (a minimum of 8 hours) prior to coming to the clinic for the LP. This means no food or drinks such as coffee, tea, milk and juice (water is permitted).

  During the procedure you will lay on your side curled up into a ball or you will sit on the edge of a chair or bed and lean forward, whichever is easier for you. The lower part of your back will be cleaned with an antiseptic. A local anesthetic will be injected into the skin of your lower back at the area of the lumbar puncture. When the area is numb, a very thin needle will be inserted into the spinal canal in the lower back, well below the level where the spinal cord ends.

After the lumbar puncture is complete, you will remain at the site for about 30 minutes. You will be given something to eat and drink before you leave. You should avoid any strenuous physical activity for the next 24 hours. This includes lifting, bending, doing housework and gardening, or doing exercise such as jogging or bicycle riding.

Baseline Visit (Visit 2)

If the screening phase shows that you are eligible to continue and participate in this study, you will return to the clinic for the Baseline evaluation.

During the Baseline Evaluation (which includes your Study Partner):

- You will be given tests of your memory and thinking and you will be asked questions about your daily functioning and your behavior.
- A physical and neurological exam will be performed.
- Your weight and vital signs (blood pressure, temperature, etc.) will be recorded.
- You will be asked about any adverse events (changes in health or any side effects) that you may have experienced since your last visit.
- A list of vitamins and medications you are currently taking will be collected.
- You will be asked questions about how you feel about being in this study.

If you continue to meet all protocol inclusion criteria and no exclusion criteria, after completion of all baseline procedures, you will be randomly assigned to receive active drug or placebo in each of the three treatment groups:

GROUP
Posiphen 60 mg Once per day or Placebo
Posiphen 60 mg Twice per day or Placebo
Posiphen 60 mg Three times per day or Placebo

You will be given a supply of study drug and will be instructed to take your first dose of study drug the morning after you have completed the Baseline visit. You will take 3 capsules per day of either study drug or placebo, with or without food, depending upon your group assignment.

You will be asked to bring all study drug blister cards (used and unused) with you to Visits 4 and 5 so that we can determine how many capsules you have taken.

If a dose is missed, do not take the missed dose later in the day. Just skip the missed dose and take the next scheduled doses.

The study drug must be used only by you and should be stored at room temperature, protected from moisture and kept out of the reach of children.

Day 14 Telephone Contact (Visit 3)

You will be contacted 14 (+/- 4) days from the baseline visit for the following:

- You will be asked about any adverse events (changes in health or any side effects) that you may have experienced since your last visit.
- A list of vitamins and medications you are currently taking will be collected.
- Your study medication compliance will be discussed.

Pre-Confinement Visit (Visit 4)

Admission for the confinement visit should occur between 21 and 23 days following the first dose of study medication. The pre-confinement visit will be conducted 1-3 days prior to admission.

During the Pre-Confinement Visit (which includes your Study Partner):

- You will be asked to bring all your used and unused study medication blister cards to this visit so your study medication compliance can be reviewed.
- A list of vitamins and medications you are currently taking will be collected.
- A physical and neurological exam will be performed.
- Blood will be drawn from a vein in your arm for routine laboratory tests to make sure you do not have any medical conditions that would interfere with your continued participation in the study.
- You will be given tests of your memory and thinking and you will be asked questions about your daily functioning and your behavior.
- You will be asked about any adverse events (changes in health or any side effects) that you may have experienced since your last visit.

Confinement Visit (Visit 5):

The confinement visit will last approximately 3 days and will consist of four phases: Admission, 36-Hour Sampling, 12-Hour Observation and Discharge. You will be provided with meals and a place to sleep during this visit.

Phase 1- Admission:

- You should arrive early in the morning after fasting overnight (a minimum of 8 hours).
- Blood will be drawn from a vein in your arm for routine laboratory tests to make sure you do not have any medical conditions that would interfere with your participation in the study.
- You will be expected to bring all your used and unused study medication blister cards to this visit so your study medication compliance can be reviewed.
- Your weight and vital signs will be recorded.
- A brief physical and neurological exam will be performed.
- Adverse events and your current vitamins and medications will be reviewed and recorded.

Phase 2 – 36-Hour Sampling:

During this phase, the following will take place over a 36 hour period:

- A brief physical and neurological exam will be performed.
- Vital signs will be collected and any adverse events and your current vitamins and medications will be reviewed and recorded.
- An intravenous (IV) line will be inserted into your vein to use for drawing blood intermittently for laboratory tests.
- A second IV line will be inserted into your vein to administer a form of the amino acid leucine called “HEAVY LEUCINE”. HEAVY LEUCINE is nearly identical to the leucine found in food except for a small difference in weight, and is harmless to humans and the environment. Amino acids are used by the body to make proteins. You will be given the HEAVY LEUCINE in order to measure certain proteins associated with AD that are made by the brain.
- You will take your study medication as instructed.
- You will undergo a Lumbar Puncture (LP) with placement of a catheter (a long, thin flexible plastic tube) for Cerebral Spinal Fluid (CSF) collection every 2 hours for a total of 36 hours over the course of your stay.

  A local anesthetic will be administered to temporarily numb a small area of skin on the lower back. A catheter (flexible tube) will be inserted through a lumbar spinal needle into the spinal fluid sac.

  After the catheter is in place, the lumbar spinal needle is removed and the catheter remains until the final CSF sample is taken. After the CSF collection process is complete, the spinal catheter will be removed by the physician/nurse.

  You will remain at bedrest throughout the CSF collection (sampling) period of 36 hours. You are allowed to use a bedside commode for toileting.

  To reduce the chance of a blood clot in your legs, you will wear anti-embolism stockings and also will be encouraged to do leg exercises periodically while lying flat in bed.

  You may be required to stay in the clinical study unit longer if the study doctor believes it is in your best interest.

  Additional physical exams and vital signs may be performed during your stay in the clinical study unit as required by the clinical study unit’s policy or at the discretion of the study doctor. The above tests may need to be repeated or additional tests may need to be performed for your safety.

- You will be provided with a special low-leucine meal plan designed for this study so that your body uses the HEAVY LEUCINE to make proteins. Many foods that you are familiar with are included in this diet, including a variety of fruits (for example, bananas, pears and peaches), vegetables (for example, tomatoes, carrots and lettuce) and certain wheat products.
- Over the course of your stay, you will be continually monitored by the study staff. You will be asked questions about any symptoms or discomfort you may be experiencing as a result of the lumbar puncture and infusions.

Phase 3 – 12-Hour Observation:

- Blood will be drawn from a vein in your arm for laboratory tests.
- You will be observed for at least 2 hours following the removal of the LP catheter.
- You will be asked if you are experiencing any pain or discomfort from the spinal tap, and given mild analgesics (Ibuprofen, Naproxen or Tylenol) if necessary.
- All of your used and unused study drug blister cards should be returned to the study staff for final drug accountability.
- You will be asked questions about how you feel about being in this study.

Phase 4 – Discharge:

- Your weight and vital signs will be collected and any adverse events will be reviewed and recorded.
- Blood will be drawn from a vein in your arm for laboratory tests.
- You will be discharged after the study staff determine you are stable to leave.

Post-Confinement 24-Hour Phone Follow-up:

You will receive a phone call from the study staff about 24 hours following discharge from the Confinement Visit. You will be asked how you are feeling and if you experienced any new adverse events since your discharge.

Early Treatment Discontinuation

If you stop participating in the study for any reason (for example, the study team feels it is in your best interest, you decide not to continue or the study is stopped), you will be asked to return to the clinic for a final evaluation visit.

This final evaluation will include all of the procedures normally performed at the Pre-confinement Visit. It is important for your health and safety to have these final procedures completed.

Your participation in the study may also be stopped by the study doctor or Sponsor without your permission. If this happens, it might be because:

- You had a bad reaction to the study drug.
- You were started on a medication that might cause you to have a bad reaction.
- The sponsor decides to stop doing the study for any reason.
- The study doctor stops doing the study for other reasons.

Summary of Study Visit Activities

The following chart summarizes the activities that will occur over the course of this study.

Visit Number	1	2	3	4	5			
Visit Name	Screening	Baseline	Phone Contact	Pre-Stay	3-Day Stay in Clinic			
Length of Visit (hours)	3-4	5-6	15 Minutes	1	72			
					Admit to Clinic	36-Hour Sampling	12-hour Observation	Discharge
Informed Consent	✓							
Personal Info, Medical & Psychiatric History	✓							
Physical & Neurological Exam	✓	✓		✓	✓	✓		
Current Vitamins & Medications Collected	✓	✓	✓	✓	✓	✓		
Vital Signs Recorded	✓	✓		✓	✓	✓		✓
Weight Recorded	✓	✓			✓			✓
Height Recorded	✓							
Blood Sampling ***	✓			✓	✓	✓	✓	✓
Urine Collected	✓							
12-Lead ECG	✓							
Memory & Thinking Skills Tests	✓	✓		✓				
Functional & Behavioral Questionnaires	✓	✓		✓				
Research Satisfaction Survey		✓					✓	
Adverse Events Collected	✓	✓	✓	✓	✓	✓	✓	✓
Lumbar Puncture (LP) ****	✓							
MRI of Brain *	✓							
LP Catheter Placement & CSF Sampling						✓		
Study Drug Dispensed		✓				✓		
Study Drug Compliance			✓	✓	✓		✓	
Telephone Contact**	✓		✓					✓
Study Partner Attend Visit	✓	✓		✓				✓

* A scan will be performed only if one had not been performed within 12 months of Visit 1

** The study team will call you within 24 hours after Visit 1 and after Discharge to see how you are feeling

*** PK sampling also obtained at 36-Hour Confinement Visit

****If an LP has been done within 90 days, the LP and samples may be used in place of Screening LP

Genetic & Biomarker Research

During this study, blood and CSF samples will be collected from you for genetic and biomarker research. The samples will be sent to laboratories contracted for the study and to the ADCS Biomarker Core at the University of California, San Diego (UCSD).

Genetic Study

Previous studies have shown that a gene called apolipoprotein E ("APOE") may influence the rate of disease progression or a subject's response to treatment. We will test your blood to see what form of the APOE gene you have. **This genetic testing is not optional.**

The results of these tests will be maintained in scientific databases for this research study. These results are important only for research - not for helping to care for you. For this reason, the results will not be released to you or your family.

No information regarding your genetic or biomarker results will be entered into your regular medical record. If you are concerned about a potential genetic disorder, you should discuss this with your primary care doctor. You and your doctor may choose to test specifically for it, but this would require additional blood samples and would not be part of this research project.

Data from your tests will not be revealed to other sites that are participating in the clinical study, family members, insurance companies, employers, or other individuals or organizations.

Although the study researchers and the study Sponsor will have access to coded individual data, any information gained from this research will be reported in publications in an anonymous summary form. Data will be stored in a locked file, and in a computer with restricted access.

Any information that could be used to potentially identify you in the computer will be stored in a separate file and encrypted. Only the researchers and their research assistants will have access to the original research data.

Your samples will be stored for up to 20 years. More research may be performed on your sample at a future date. You will not be notified at the time this additional research is conducted, nor will any additional informed consent be obtained. This research will be limited to the health information recorded by your study doctor or generated from any blood samples collected from this study. You will not be contacted in the future to provide any further information.

By signing this consent form, you give the Sponsor and other commercial or academic third parties that collaborate with the Sponsor, permission to use the material obtained from your sample for pharmacogenetics research. At any time for any reason, you may withdraw consent for this genetic testing and request that your sample be destroyed with no further testing being performed.

Sample Storage & Future Use

With your consent, we would like to store your DNA sample for future research studies related to Alzheimer's disease and other neurodegenerative disorders. If you decide you do not want to have your DNA sample stored for future research, you may still participate in this study.

Storage of your remaining blood and CSF samples is required for this study and it is **not optional**. If you decide that you do not want your blood and CSF samples stored for future research, you may not participate in this study.

Your samples will be stored by code number and no identifying information will be included with them. Samples will be stored indefinitely at the ADCS Biomarker Core and may be shared with other researchers studying AD or aging.

If your samples are sent to other researchers, they will be identified only by a code number and descriptive data (such as your age and gender). No other personal identifying information will be attached to your samples, so it will not be possible to identify you from any of the samples.

MRI Image Storage & Future Use

Your MRI images will be sent to the ADCS and will be analyzed by researchers at other institutions. ADCS investigators will maintain your imaging data and be responsible for deciding how it will be used for future research.

Study investigators may make some of this data available to investigators at other scientific institutions for research purposes.

Your name and all links to your identity will be removed from the data before it is shared. Your imaging data will be labeled with a coded research identifier to protect your identity.

Will this research data be shared?

Data from this research will be shared with other researchers and the FDA. Data sharing is important for further translation of research results into knowledge, products and procedures to improve human health. All links with your identity will be removed from the data before it is shared.

What are the risks and possible discomforts from being in this research study?

Taking Posiphen daily may involve risks that are not known at this time due to the investigational nature of this study. Some of these unknown risks may be life-threatening or result in death. However, you will be told of any new risks or significant findings that develop during the course of this study.

You will be assigned to a study group at random (by chance). Your assignment is based on chance rather than a medical decision made by the researchers. The study group you are assigned to might not be the group you would prefer to be in. Your assigned study group might also prove to be less effective or have more side effects than the other study group(s), or other treatments available for your condition.

Participation in this study may involve some added risks or discomforts, which are outlined below.

Risks of Study Drug (Posiphen)

To-date, a total of 101 individuals have taken Posiphen. The most common (occurring in 2 or more subjects) side effects reported after receiving Posiphen have included the following:

- Dizziness
- Headaches
- Abnormal dreams
- Nausea
- Vomiting
- Feeling warm
- Heart rate increased
- Constipation
- Fainting
- Orthostatic hypotension

It is important to remember that Posiphen has been studied in a limited number of people. Therefore, Posiphen may involve other risks, including life threatening risks that are not known at present. Because Posiphen is a drug that works on the nervous system, you should notify your study doctor immediately if you experience any changes in your thinking, behavior or mood.

Risks of Drugs that Reduce β-Amyloid in the Brain

Posiphen is designed to reduce β-amyloid protein in the brain. With some other drugs that reduce β-amyloid protein cerebral vascular edema (swelling on the brain) was observed. In particular, in a clinical study examining the ability of an experimental vaccine to reduce the amount of β-amyloid protein in the brain swelling was observed in 12 individuals. The swelling in these patients was not permanent. Brain swelling increases pressure inside the skull. This pressure can prevent blood from flowing to your brain, which deprives it of the oxygen it needs to function. Swelling can also block other fluids from leaving your brain, making the swelling even worse. Damage or death of brain cells may result. To date brain swelling has not been observed after taking Posiphen.

Symptoms of brain swelling vary, depending on the severity and the cause. Usually they begin suddenly. You may notice any of these symptoms:

- Headache
- Neck pain or stiffness
- Nausea or vomiting
- Dizziness
- Irregular breathing
- Vision loss or changes
- Memory loss
- Inability to walk

- Difficulty speaking
- Stupor
- Seizures
- Loss of consciousness

In the event you experience any of these symptoms, please contact your doctor and [SITE INVESTIGATOR NAME] immediately.

Risks of Lumbar Punctures

In total, up to 142 mL - approximately 9 tablespoons of CSF may be taken during the entire study. Your body will make up for this loss.

During the lumbar puncture procedure, you may have temporary pain and discomfort in your back.

Headache may occur in about 5% of people who undergo a lumbar puncture. Less commonly, in about 1 - 4% of participants, is a persistent low-pressure headache that may develop, probably due to leakage of CSF. If the headache persists it may require additional treatment.

Uncommonly, a blood patch (injection of some of your blood into the lumbar puncture site to patch the CSF leak) may be required and should relieve the headache immediately.

Although very rare, it is possible that you may have an allergic reaction to the local anesthetic (lidocaine 1%) used for the lumbar puncture. An allergic reaction could cause swelling and a rash on your skin where the anesthetic was injected. Please tell us if you have ever had a reaction to local anesthetic before (such as when you were visiting the dentist).

Potential but rare risks of lumbar puncture include infection, damage to nerves in your back and bleeding into the CSF space. The risk of these is much less than 1%. To minimize these risks, the lumbar puncture will be performed by Dr. [INSERT NAME OF DOCTOR WHO WILL BE PERFORMING LP HERE] or by a neurologist specifically trained in the procedure.

Risks of CSF Sampling

The risks associated with continuous CSF sampling are similar to those associated with a single lumbar spinal tap.

The most common side effects of this procedure are headache and backache. If a headache occurs, it is generally relieved by drinking fluids and lying down. If necessary, you may receive a pain reliever such as Acetaminophen or one or more doses of Caffeine through your IV line.

Headaches can recur for several days, although on rare occasion headaches can last longer - up to a couple of weeks.

If you experience a persistent headache, it is possible that a blood patch procedure will be performed. The rate of post–lumbar puncture headache requiring a blood patch is about 10% in older individuals. This involves the injection of a small amount of your own blood into the region of the original tap but not into the CSF fluid space. The blood-patch is performed by an anesthesiologist and has been effective in relieving headache in up to about 95% of cases.

In rare cases, this procedure may need to be repeated. This may be done under X-ray guidance at the discretion of the anesthesiologist to guide the injection of blood. Should you experience a headache during the period after the lumbar spinal tap, you must notify the study team.

Most people experience only the minor discomfort of a needle prick when local anesthetic is administered. Others experience a few moments of mild to moderate pain similar to that experienced when an injection is received. A hypersensitivity or allergic reaction to the local anesthetic may occur. The collection of CSF is usually painless.

Another discomfort that can occur following a lumbar spinal tap is a brief pain or tingling sensation in either leg, hip, buttock or groin area. This is caused by a brief stimulation of a nerve and ends quickly with no further complications.

This discomfort may also occur once the spinal catheter is in place and is reversible with change in position, adjusting the catheter or removing the catheter.

On rare occasions, a temporary weakness of the eye muscle that moves the eye from side to side may develop, producing double vision. This complication has been temporary, and normal vision has been restored.

Other complications are rare and include nerve root damage, epidural (the area outside the covering of the spine) or subdural (spinal) bleeding, infection, paralysis or death.

All precautions will be taken to minimize these risks. Subjects will be monitored for associated symptoms of infection: neck stiffness, headache, increased irritability, nausea, light sensitivity and fever following the procedure.

Risks of Blood Draws & IV Line Insertions

Drawing blood from a vein in your arm and inserting an intravenous (IV) line into your arm poses a small risk of infection, temporary pain, blood clot or bruising at the site of the needle stick. Some people may feel light-headed, or experience upset stomach or fainting when their blood is drawn.

To minimize these risks, experienced medical personnel will handle all the blood drawing and IV line insertion procedures and sterile conditions will be maintained.

In total, 215 mL – approximately 14 tablespoons of blood - may be taken during this study. Your body will make up for this loss.

Risks of MRI Scans

An MRI may cause possible discomfort for people due to the loud banging made by the machine and the confined space of the testing area. There is also a risk of injury if metal is brought into the imaging room, which might be pulled into the MRI magnet.

Risks of ECGs

There is no pain or discomfort during an ECG; however, removing the pads may cause some irritation to your skin.

Risks of Reproduction

It is not known if the study drug may affect an unborn or nursing baby. If you are pregnant or breastfeeding, you cannot be in this study.

Women who are capable of having children are excluded from participation in this study. If you are a woman, you must either 1) be two years post-menopausal or 2) have had a documented surgical sterilization procedure.

The effects of Posiphen on the developing fetus are unknown and there is a possibility it may cause physical or mental damage. There may be risks to an unborn baby you father during or after the study.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active and are not surgically sterile, you must agree to use a barrier method of birth control (such as a condom with spermicide) from the time you start taking the study drug until 30 days after you receive the last dose of Posiphen.

If you (or your partner) becomes pregnant during this time period, you must notify the study doctor or study staff immediately. The study doctor may ask for information about the pregnancy and the birth of the baby. The study doctor may share this information with the Sponsor or other parties listed in the section about confidentiality.

If you are not willing to use acceptable birth control, you should not participate in this study or sign this consent form.

Risks of Genetic Testing

Variation in some genes is known to be directly related to risk of certain illnesses. Under some circumstances, it can be a risk for genetic information to be known by others. In some cases, knowledge of genetic information could have negative psychological consequences or could affect access to or retention of certain benefits or entitlements. For example, the information could potentially be used against subjects if it were revealed to insurance companies or potential employers.

A U.S. Federal law called the "Genetic Information Nondiscrimination Act" (GINA) generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote or fire you or when setting the terms of your employment.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance or long-term care insurance.

You will not get the results of the genetic portion of the study nor will the results be made available in your medical record.

Furthermore, the researchers have adopted strict privacy and confidentiality procedures for maintaining your genetic information as described in this consent form.

Risks of Loss of Confidentiality

Study personnel will not release your study information to your doctor without your permission, and will code your study information to protect your confidentiality.

However, it is possible that information about your participation in this study could enter your medical record, particularly if you experience an adverse event requiring treatment.

It is possible that information about your amyloid status or participation in this study could influence your ability to obtain life insurance, health insurance, or long-term care insurance or affect your future employability.

To help us protect your privacy, a Certificate of Confidentiality (Certificate) for this study has been obtained from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally-funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of [INSERT STATE].

Risks of Placebo

If you receive placebo as your study drug, you may experience memory problems consistent with AD and aging.

Risks of Testing & Questionnaires

Repeated evaluations of mood and mental status may be slightly frustrating or produce fatigue and boredom.

Unknown Risks & New Information

In addition to the side effects already described, the study drug and the study procedures may have other unknown risks. As with any new medicine, there is a risk of rare or previously unknown side effects, and/or a chance that Posiphen might interact with other medicines. You must tell your study doctor if you experience any side effects.

As with any drug, you may experience an unexpected allergic reaction that could be life-threatening. Symptoms of an allergic reaction can include, but are not limited to:

- Rash
- Having a hard time breathing
- Wheezing when you breathe
- Sudden drop in blood pressure
- Swelling around the mouth, throat or eyes
- Fast pulse
- Sweating

If you suffer a serious or lasting injury because of your participation in this study, it may affect your ability to obtain private health insurance, your employability and/or your quality of life.

If you should experience a skin reaction during your participation in the study, whether or not the reaction causes you discomfort or you believe the reaction is serious, a photograph of the area where the reaction appears may need to be promptly taken for evaluation and assessment purposes, as determined by the study doctor. These photographs, if taken, will remain in confidential files and your identity will not be revealed.

New information about Posiphen may become available during the study. If this happens, your study doctor will tell you about the new information, and [he/she] will talk to you about whether you want to remain in the study.

What are the benefits of taking part in this study?

Participation in this study may help to improve your condition, but it is also possible that your condition may not improve or could worsen. There is no guarantee that you will personally benefit by participating in this research study.

Your participation in this study may help the investigators learn more about the safety and benefits of Posiphen for Alzheimer's disease to help other people who have a similar medical problem in the future.

What other choices do I have if I do not take part in this study?

If you are currently experiencing memory problems, there are 5 drugs approved for the treatment of Alzheimer's disease:

- Donepezil (Aricept®)

- Tacrine (Cognex®)
- Galantamine (Razadyne®)
- Rivastigmine (Exelon®)
- Memantine (Namenda™)
- Aducanumab (Aduhelm™)

Thus, alternatives to participation in this study include the possible use of one of these approved medications.

Because study results might be affected, participation in any other clinical studies will not be permitted until your participation in this study has ended.

Another alternative is not to participate in this study and to continue under standard medical care, which may include receiving some of the above listed medications for memory problems and AD.

Will my medical information be kept private/confidential?

Research records will be kept as confidential as possible within the limitations of state and federal law. The study staff and Sponsors will handle your personal health information in a confidential manner.

Federal Privacy Regulations require that you authorize the release of any health information that may reveal your identity.

For this research study, this includes information in your existing medical records needed for this study and new information created or collected during the study.

The persons and entities that you are authorizing to use or disclose your personal health information may include the:

- **Study doctor**
- **Study staff**
- **Institution**
- **Institution's IRB**
- **Alzheimer's Disease Cooperative Study (ADCS)**
- **Other ADCS research sites participating in this study and**
- **Laboratories used for this study**

In order to analyze the data collected during this research study, all of the health information generated or collected about you during this study may be inspected by the study Sponsor and its authorized agents, the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) agencies and the Institutional Review Board (IRB).

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed.

Once your personal health information is released it may be re-disclosed, at which point your health information will no longer be protected by federal privacy regulations.

The findings of this research will be presented at meetings or in publications; however, neither your name nor identity will be disclosed in those presentations.

You have the right to review and copy the health information collected about you, however, you will not be allowed to look at your study-related information until after the research is completed.

This authorization will have no expiration.

What are the costs of taking part in this research study?

There will be no costs to you for participation in this study.

Procedures related to the study and study drug will be provided at no cost to you.

Will I be paid for taking part in this research study?

You may receive up to [INSERT AMOUNT] for participation in this the study. This money covers the costs for time spent at the clinic and travel expenses to and from the clinic.

If you choose to leave or are withdrawn by the study staff before finishing all study procedures, you will be paid a lesser amount that is based on the completed visits or procedures. You will also receive a hand-crafted quilt donated by the Quilt Guild for study participation.

No other payment will be offered to you. You will receive your payment within 2 weeks of your final visit.

What happens if I am injured as a result of taking part in this research study?

All forms of medical findings and treatments – whether routine or experimental – involve some risk of injury. In spite of all safety measures, you might develop medical problems from participating in this study.

You must report any suspected illness or injury to the study doctor immediately. If such problems take place, the [SITE INVESTIGATOR'S INSTITUTION] will provide emergency medical treatment and will assist you in getting proper follow-up medical treatment.

If you require medical treatment for an untoward event, the company that manufactures the drug (Annovis Bio, Inc.) in consultation with the study doctor, will pay the reasonable and customary costs of such treatment only if it is determined that the untoward event occurred as a result of manufacture of the study drug and the costs of treatment are not covered by any other health insurance, government health program or other third party providing coverage for health care.

Neither financial compensation nor reimbursement for such things as pre-existing conditions, illness or disease unrelated to study drug, lost wages, property damage, disability, or discomfort is available.

The National Institute on Aging and the Alzheimer's Disease Cooperative Study do not provide compensation for any other type of research-related injury related to participation in this study. IN ADDITION TO THIS STATEMENT, ADD YOUR INSTITUTION'S SUBJECT INJURY CLAUSE HERE (you will / will not pay for subject injury, etc). By signing this consent form you do not give up any of your legal rights.

If I have questions or concerns about this research, whom can I contact?

If you have any questions regarding this research or if you believe that you may have experienced a research related injury or a reaction to the study drug, you should contact Dr. [Insert Site PI Name] (study doctor) at [TELEPHONE].

OFFICE], at [TELEPHONE] for more information about this or to report research-related problems.

Is participation in this study voluntary?

Your participation in this research study is entirely voluntary. You have the right to refuse to participate, or may discontinue participation in this study at any time without jeopardy to the medical care you receive at this institution.

You have the right to not sign this form that allows us to use and share your health information for research; however, if you don't sign it, you cannot take part in this research study.

You have the right to withdraw your permission to use or disclose personal information about your health. If you choose to withdraw your permission, you must notify Dr. [Insert Site PI Name] **in writing. Dr. [Insert Site PI Name]'s mailing address is:**

(Insert Address)

Dr. [Insert Site PI Name] will still be able to use the information collected about you prior to your withdrawal from the study. Information that has already been sent to the Sponsor cannot be withdrawn.

STATEMENT OF CONSENT

You have read (or have had read to you) the above description of this research study. You have been informed of the risks and benefits involved, and all of your questions have been answered to your satisfaction. By signing this form, you voluntarily consent to participate in the research study and you authorize the use of your bodily fluid samples for the research described above.

Unless you authorize the use and disclosure of your personal health information, you cannot participate in this research study. If you refuse to give your authorization, your medical care will not be affected.

You will receive a copy of this consent form.

	Yes	No	Subject Initials
You voluntarily agree to participate.	☐	☐	_____

Sample Storage

You agree that your **DNA samples** may be stored and used for future research. (Optional)	☐	☐	_____
You agree that your **Blood samples** may be stored and used for future research. (Not Optional)	☐	☐	_____
You agree that your **CSF samples** may be stored and used for future research. (Not Optional)	☐	☐	_____

Study Participant Name (print)	Signature	Date
Person Obtaining Consent (print)	Signature	Date
Legal Representative / Next of Kin If applicable (i.e. spouse, child, sister) (print)	Signature	Date
Witness Name (print)	Signature	Date

STUDY PARTNER INFORMATION & CONSENT

As the participant's study partner, you have important tasks that need to be carried out in order for the study to be conducted in the safest and best manner possible. These responsibilities include:

- You must have regular contact with the participant a minimum of 10 hours per week and provide supervision of drug administration as needed.
- You must attend the entire screening and baseline visits. You should also stay for the first three hours of the confinement visit and return to drive the participant home.
- You are an important source of information about the participant. You must agree to be asked questions about your relationship with the participant, as well as their health, memory, daily functioning and behavior in order to find out whether there are any changes in the participant.
- You must be able to make sure that the study participant is taking the study drug as directed.

If for some reason you become unable to carry out your responsibilities, please tell the study team immediately. You may be asked, if possible, to select a substitute who can take over your duties.

You have read all the preceding information which describes both the participant's participation in the study and your involvement as the participant's study partner. The study has been explained to you in detail. All your questions have been answered to your satisfaction.

	Yes	**No**	**Study Partner's Initials**
You voluntarily agree to participate as a Study Partner.	☐	☐	_____

Study Partner's Name (print)	**Signature**	**Date**

Person Obtaining Consent (print)	**Signature**	**Date**

California Site Only: Insert the Experimental Bill of Rights