Participant Name: MRN or DOB: Participant Identification

Research Consent Form

Certificate of Confidentiality Template
Version Date: May 2025

Protocol Title: An open-label, single ascending dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intrathecally administered PrP-siRNA in adults with symptomatic prion disease and in pre-symptomatic adults at genetic risk for prion disease.

Protocol Principal Investigator: Eric Vallabh Minikel, PhD

Site Principal Investigator: [Insert site name]
NeuroNEXT Clinical Study Site: [Insert site number]
Clinical Study Site: [Insert site name]

Description of Participant Population: Symptomatic patients diagnosed with prion disease

DRUG DOSE/ ARM 2 / PrP-siRNA Treatment

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "participants." This term will be used throughout this consent form.

[Name of CSS Site] is [description of CSS site]. We are doing this research as part of the NeuroNEXT Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), which is supported by the National Institute of Neurological Disorders and Stroke (NINDS).

Some of the people who are eligible to take part in this study may not be able to give consent to take part because of their medical condition. Instead, we will ask the person's authorized representative to give consent. Throughout the consent form, "you" always refers to the person who takes part in the study.

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Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within [CSS Site] now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

If you decide to join this research study, you will receive an injection of the study drug, PrP-siRNA, into your spinal fluid. You will also undergo blood draws, lumbar punctures for spinal fluid collection, physical exams and mental and cognitive tests, and 2-day hospitalization to monitor for potential drug side effects.

There are currently no human data supporting any benefits to you individually from taking part in this research study. The main benefit is the opportunity to contribute to research and produce generalizable knowledge about PrP-siRNA and about prion disease. This drug has been studied in animals but has not yet been tested in people, so its side effects in people are not known. In a single dose toxicology study, gliosis - an increase in the number of glial cells in the brain - was observed in some animals treated with this drug at doses 3-8 times higher than the dose you may receive. This is a not uncommon finding in drugs infused directly into the spinal cord. The gliosis did not appear to have any behavioral effects on the animals and was observed only 1 day after dosing; no animals still had this change at 28 days after dosing. No other adverse effects were observed in the toxicology studies. Nonetheless, potential side effects in human are an important risk you should consider.

There exists a risk that this drug might increase the time you survive without improving your symptoms. In the context of neurodegenerative illness, some patients and their study partners may consider increased lifespan with low quality of life to be a harm rather than a benefit.

Many clinical trials specifically exclude individuals who have recently taken part in previous clinical trials. There exists a risk that a clinical trial for another potential drug for prion disease will open recruitment in the future, and that you will be ineligible to participate because you already participated in this study.

There are various other risks associated with study procedures, data security, genetic information, and incidental findings. These risks are discussed in more detail further below.

To take part in this study, participants must have a study partner who can assist with study visits. The study partner may be, but is not required to be, the legally authorized representative (LAR) who obtains consent.

You will not be paid for taking part in this research study. You will find more information about the payment amount for each visit and a plan if you do not complete all study visits later in this form.

If you have any questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Insert name and academic degrees] is the person in charge of this research study. You can call him/her at **[Insert phone number] [Insert when person is available M-F 9-5 or 14/7]**. You can also call **[Insert name(s)] at [Insert phone number(s)] [Insert when each person is available M-F 9-5 or 24/7]** with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call **[Insert name(s)] at [Insert phone number(s)].**

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB. You can call them at [redacted].

You can talk to them about:

- Your rights as a research participant
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study

Detailed Information

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

Why is this research study being done?

Prion disease is always fatal and there is currently no approved treatment by the U.S. Food and Drug Administration. A new compound called PrP-siRNA is being developed as a potential treatment for prion disease, but we do not yet know whether it is safe or effective. Testing this drug can only be done in research studies. In this research study we want to learn about the drug's safety, meaning whether it causes adverse side effects, and its pharmacology, meaning how it behaves in the body.

How long will you take part in this research study?

If you decide to join this research study, it will take you about 28 weeks to complete the study. During this time, we will ask you to make 8 study visits to [CSS Site].

Who will take part in this research?

We are asking you to take part in this research study because you have been diagnosed with prion disease. Prion disease is a fatal, usually rapid, neurodegenerative disease caused by misfolding of prion protein (PrP) in the brain. Forms of prion disease are known as Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Straussler-Scheinker disease (GSS), or variably protease sensitive prionopathy (VPSPr).

About 30 participants will take part in this research study. About 5 participants will take part at **[Name of Hospital].**

The U.S. National Institutes of Health (NIH) are paying for this research study to be done, through a program called the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT).

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What will happen in this research study?

The purpose of this research project is to test the safety, metabolism, and activity of the study drug, PrP-siRNA, a small interfering RNA oligonucleotide drug. This research project seeks to find out what the side effects are, how your body copes with this drug and if this drug is active against prion protein, PrP, in the brain. The drug, PrP-siRNA, is designed to bind and cut up the messenger RNA encoding PrP, thus preventing the protein from being formed. PrP misfolding is what causes prion disease. If less PrP is produced in the first place, it is hoped that less PrP will misfold, and neurodegeneration will be slowed down. Whether PrP-siRNA can achieve this is still unknown.

It will take you about 28 weeks to complete this research study. During this time, we will ask you to make 8 study visits to [CSS Site].

You will be required to have a study partner or LAR throughout your participation in this study. This person must see you at least once a week and be able to travel to each study visit with you.

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures. The drug administration and monitoring period will take place at [CSS Site]. The screening visit and post-dose follow-up visits will take place at [CSS Site].

Visit 1 – Screening
The Screening Visit will take about 4-5 hours. During this visit, we will do some tests and procedures to see if you qualify to take part in this research study. The study doctor will review the results of these tests and procedures. If you don't qualify, the study doctor will tell you why. At this visit we will:

- Have you review and sign the informed consent form(s) with a study investigator
- Assess inclusion and exclusion criteria
- Ask you about your medical history and medications you are currently taking
- Review your current prion disease symptoms
- Do a physical and neurological exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample and complete an ECG for safety.
- Ask your study partner to answer questions about your ability to perform day-to-day tasks

- Test your blood or urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- Complete a Columbia-Suicide Severity Rating Scale (CSSR-S)
- Complete a Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Complete a Montreal Cognitive Assessment (MoCA)
- Complete a MRC-PDRS Assessment
- Undergo magnetic resonance imaging (MRI) or (CT) to obtain a scan of your brain

Visit 2 – **Baseline** Drug administration and monitoring
At this visit, you will be admitted to the hospital for at least 24 hours. During this visit, you will receive the investigational drug and then undergo careful monitoring for safety of the drug.

- Review inclusion and exclusion criteria
- Review your current prion disease symptoms
- Do a physical and neurological exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample for:
    - Clinical safety labs
    - Research analysis
    - Genetic testing
- Ask your study partner to answer questions about your ability to perform day-to-day tasks
- Test your blood or urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- Perform a lumbar puncture to collect a spinal fluid sample for research analysis.
- Ask about medications you are currently taking
- Complete a Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Complete a Montreal Cognitive Assessment (MoCA)
- Complete a MRC-PDRS Assessment
- Inject the investigational drug via a lumbar puncture.
- Use an electrocardiogram (ECG) to monitor your heart.
- Observe you over 1 night in the hospital to identify any adverse side effects

Visits 3-4 – Post-dose monitoring
At these visits, we will monitor for side effects, disease progression, and the presence of the drug in your body, and we will make measurements to determine whether the drug is doing what it is designed to do.

- Ask about any medications you are currently taking
- Review your current prion disease symptoms
- Do a physical and neurological exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample for:
    - Clinical safety labs
- Ask your study partner to answer questions about your ability to perform day-to-day tasks
- Complete a Columbia-Suicide Severity Rating Scale (CSSR-S)

Visits 5-8 – Post-dose monitoring
At these visits, we will monitor for side effects, disease progression, and the presence of the drug in your body, and we will make measurements to determine whether the drug is doing what it is designed to do.

- Ask about any medications you are currently taking
- Review your current prion disease symptoms
- Do a physical and neurological exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample for:
    - Clinical safety labs
    - Research analysis
- Ask your study partner to answer questions about your ability to perform day-to-day tasks
- Complete a Columbia-Suicide Severity Rating Scale (CSSR-S)
- Complete a Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Complete a Montreal Cognitive Assessment (MoCA)
- Complete a MRC-PDRS Assessment
- Undergo magnetic resonance imaging (MRI) to obtain a scan of your brain (Visit 6 only)
- Perform a lumbar puncture to collect a spinal fluid sample for research analysis.
- Administer exit questionnaire (Visit 8 only)

All visits are intended to be conducted in person, and the drawing of blood and CSF is a critical part of both the safety monitoring and research for this study. Nonetheless, if you become unable to visit us in person for one or more visits, we may ask you to make a visit via videoconference instead.

After you complete the study

Your DNA sample may be banked and used for future prion disease, and related neurodegenerative disorders, genetic research. Usually, researchers study just a few areas of your genetic code that are linked to a disease or condition. If whole genome analyses is performed in the future, all or most of your genes are looked at and used by researchers to study links to prion disease.

In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

Study Procedures

Lumbar Punctures: There will be 5 lumbar punctures in this study. A lumbar puncture (LP) is commonly called a spinal tap. At each of the 5 LPs, we will draw cerebrospinal fluid (CSF) using a needle inserted in the lower back for analysis of biomarkers. Lumbar punctures will be performed under local anesthesia to numb the area. We will analyze collected CSF to assess for molecules that may be associated with prion disease. At the drug administration (visit 2) LP, in addition to collecting CSF, we will inject the investigational drug.

LPs may be performed by the Interventional Radiology (IR) department at Visits 3-6 only, subject to the site's discretion. IR may not be used at Baseline (Visit 2). If the LP cannot be performed at Baseline for any reason, the participant will be excluded from the study.

Magnetic resonance imaging (MRI) or CT Scan: MRI is an imaging procedure that uses a powerful magnetic field, radio waves, and a computer to generate high-resolution images of the body without using radiation. The protocol requires participants to remain still within a relatively confined space during the scanning session, and the scanner makes knocking and beeping sounds

as it takes images. The MRI scan is used to determine eligibility for this study. If you do not have recent brain imaging available, a CT scan may be performed during screening as an alternative to an MRI to ensure there are no current safety concerns.

ECG (electrocardiogram): This test checks the electrical activity of your heart. We will place several small, sticky pads on your chest, arms, and legs. Each pad has a wire attached. The wires connect to a machine that makes a recording of your heart rhythm. This painless test takes about 15 minutes.

Neurological Examination: Checking your senses, reflexes, strength, balance, and coordination at each in person visit. A prion disease checklist will also be administered at each exam to capture prion-related symptoms.

Physical Examination: The physical exams include examining your heart, lungs, abdomen, and skin. This will occur at each in person visit.

Blood Draws: We will draw blood from a vein in your arm for standard laboratory tests and for research purposes. Blood will be drawn for safety checks at your first visit (if not done elsewhere) and may include using a finger stick test to obtain a drop of blood to check your coagulation. We will measure components of your blood that may be affected by prion disease and how these may be related to your disease and disease progression. At each visit, we will draw about 40 mLs (about 2.7 tablespoons) from your vein. In total, approximately 8 tablespoons of blood will be collected over the course of the entire research study (about 28 weeks).

Cognitive Testing (MoCA and MRC-PDRS): We will ask you to complete certain tasks in order for us to understand how your brain is performing and to make comparison of your performance at different points during the study.

Neuropsychiatric Inventory- Questionnaire (NPI-Q): This questionnaire measures dementia-related behavioral symptoms and is used to assess changes in psychological status. The NPI-Q examines 12 sub-domains of behavioral functioning including: hallucinations, delusions, agitation, dysphoria (state of dissatisfaction), anxiety, euphoria (state of intense happiness), apathy (lack of interest), disinhibition, irritability, aberrant motor activity, eating abnormalities, and night-time behavioral alterations. The NPI-Q will be administered to your study partner by a qualified study staff member.

Columbia Suicide Severity Rating Scale (C-SSRS): One of the study staff members will ask you questions about possible suicidal thinking and behavior. This questionnaire will take about 5-10 minutes to complete.

Biobank Repository: Additional blood will be collected for banking for future research. This research includes biomarkers, genetic, and study drug testing.

In addition, we will collect cerebrospinal fluid, blood, demographics, neurocognitive and medical history, vital signs, neurological and clinical assessments, physical examination, adverse event review, concomitant medication information, Columbia Suicide Severity Rating Scale, ECG, clinical safety labs, brain MRI images, MRC-PDRS, and/or cognitive/behavioral/function assessment. If you agree, these samples and data will be stored in the Prion Biobank. Your decision to participate does not affect your eligibility for this study or future studies.

How may we use and share my samples and health information for other research?

The information we collect in this study may help advance other research related to prion disease. If you join this study, we may remove all information that identifies you (for example, your name, medical record number, and date of birth) and use these de-identified samples and data in other research. During the study, a designated central repository will receive, manage, and distribute the research samples for the trial research studies. Upon completion of the study, samples will be donated for continued research to biorepositories such qualified researchers at the Broad Institute, Mass General Brigham institutions, as well as non-Mass General Brigham academic institutions and for-profit companies or other similar biorepositories. It will not be possible to link the information or samples back to you. Information and/or samples may be shared with investigators at our hospitals, at other academic institutions or at for-profit, commercial entities. You will not be asked to provide additional informed consent for these uses.

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at Mass General Brigham for other research related to prion disease. If we share your samples and/or health information with other researchers outside of Mass General Brigham, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a locked file on a password protected computer.

Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to prion disease?

☐ YES ☐ NO Initial _____

Prion disease is a terminal disease. It is possible that some participants will pass away due to disease progression during this trial. If so, families may choose to donate their loved one's brain to the National Prion Disease Pathology Surveillance Center (NPDPSC) in Cleveland, Ohio, for autopsy. Autopsy data from clinical trials like this one are valuable for understanding the distribution and activity of the drug in the human brain. If you choose to donate your brain to NPDPSC, you will sign a separate consent form with NPDPSC to allow them to analyze your brain tissue. In order to link your autopsy data to data from this clinical trial, we will share identifiable information about you from this trial with NPDPSC. Your data and samples from NPDPSC may then further be shared with companies involved in analyzing the tissue, but this sharing will be done using only de-identified codes and not your identifiable information. Only NPDPSC will have access to your identifiable information.

Will you get the results of this research study?

No. The research study we are doing is only a stepping stone in understanding prion disease and in evaluating PrP-lowering divalent siRNA PrP-siRNA as a potential drug. The results of the overall research study may be published in order to share what we have learned with the research community. However, no information about the results of your individual participation in the research study will be given to you or your doctor. Tests done for the research using your samples will not be useful in directing your medical treatment. The results of the tests will not be placed in your medical record.

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

Risks of Taking PrP-siRNA

This drug has never been tested in humans before, only in animals, and it is possible that the drug will prove toxic or have adverse side effects. This drug has been studied in animals but has not yet been tested in people, so its side effects in people are not yet known.

In a single dose toxicology study, gliosis - an increase in the number of glial cells in the brain - was observed in some animals treated with this drug at doses 3-8 times higher than the dose you may receive. This was usually observed only 1 day after dosing; no animals still had this change at 28 days after dosing. 1 animal in these studies showed an injection site reaction, with both gliosis and some damage to neurons surrounding the immediate site of the injection. These adverse effects were observed only under a microscope; no behavioral effects on the animals were observed. No other adverse effects were observed in the toxicology studies.

There exists a risk that this drug might increase the time you survive without improving your symptoms. In the context of neurodegenerative illness, some patients and their study partners may consider increased lifespan with low quality of life to be a harm rather than a benefit.

There may be other risks of PrP-siRNA that are currently unknown.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing any other life-threatening symptoms, call 911 immediately.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of PrP-siRNA on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). All other female participants must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below. You must use birth control for the entire study and for at least 6 months after your last dose of study drug.

Acceptable birth control methods for use in this study are:

- hormonal methods, such as birth control pills, patches, injections, vaginal rings, or implants
- barrier methods (such as a condom or diaphragm)
- intrauterine device (IUD)
- abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant before drug administration, you may not proceed with drug administration. If you become pregnant after drug administration, you must stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Risks of Taking PrP-siRNA with Other Medications

Please consult the study investigator before taking any blood thinners such as warfarin or apixaban while you are in the study. Taking these drugs may increase the risk of complications from a lumbar puncture.

For your safety during this study, call your study doctor BEFORE you take any:

- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

No people have ever have taken PrP-siRNA before. It has only been tested in animals. Therefore, we don't know about all the side effects that can happen when taking this drug together with other medications.

Risks of Blood Draws

You may experience bruising (a black and blue mark) or pain from the needle site during blood draws. There is also a small risk of infection, lightheadedness, and/or fainting, however a nurse or lab professional will monitor you for these symptoms.

Risks of Lumbar Puncture

This trial will involve lumbar punctures (LP) to inject the drug and to retrieve spinal fluid for testing. Although LPs are generally regarded as being safe, they do carry potential risks. Up to 20% of people who undergo a lumbar puncture develop a headache afterwards. Post lumbar puncture headaches typically begin within 72 hours of the LP and usually last less than 5 days. There is also a very slight risk of infection or bleeding due to the procedure.

Although very rare, it is possible that you may have an allergic reaction to the local anesthetic used, like lidocaine. An allergic reaction would cause swelling and a rash on your skin where the anesthetic was injected. Please alert the study staff if you have ever had a reaction to local anesthetic before (especially if this occurred with a dental procedure). To minimize these risks, the LP will be performed by a trained medical professional.

Risks of Fluoroscopy and Radiation Exposure

In this study, you may undergo imaging using fluoroscopy which is a type of medical imaging that shows a live X-ray image on a monitor, like an X-ray "movie." This live X-ray image is usually used to see movement of a body part. Some lengthy fluoroscopy studies have the potential to result in an injury to the skin. Skin injuries are very rare and usually happen only during long or complicated procedures or when problems cause the procedure to take longer than expected. Skin injuries are usually limited to reddening of the skin (like sunburn) but may also involve loss of hair or skin blistering. Like a sunburn, skin injury may be uncomfortable or painful. Rarely, there may be permanent skin damage. Skin injury may happen within days or weeks of the fluoroscopy procedure or may occur months or rarely, a year later. If you notice any changes to your skin, tell the study staff right away.

Risks of Imaging Procedures

MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube of an MRI scanner. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study.

The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped. Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

Risks Related to Imaging Procedures / Ionizing Radiation Exposure

If you take part in this research, you will be exposed to very small amounts of ionizing radiation, which for example, is the type of radiation in X-rays. If you are interested, please go to https://online.fliphtml5.com/hwbaz/oqkh/#p=1 to learn more about radiation. In this study, ionizing radiation comes from CT scans and interventional radiology (IR).

Everyone gets small amounts of natural radiation, called background radiation. This comes from outer space and from rocks and minerals in the soil. The amount of natural background radiation depends on where you live.

The amount of ionizing radiation you will get by participating in this study is very small and is lower than what you get from background radiation. This ionizing radiation exposure is not required for your medical care and is necessary only to complete the study.

Scientists are not sure as to the actual risk of this amount of exposure. It is very low, and there may be no risk at all. Since the effects of ionizing radiation can add up, it is important to

consider your past radiation exposure in considering your risks. If you would like more information about the ionizing radiation exposure associated with this study, please speak with the study doctor.

If you are pregnant, you cannot be in this research study. You may be asked to take a pregnancy test (urine or blood test) to see if you are pregnant before joining the study. Pregnancy tests are good at telling if you are pregnant but are not always correct, especially in early pregnancy. If you join this study, you should use contraception to keep from getting pregnant while you are in the study. If you get pregnant while you are in this study, or if you think you are pregnant, please tell the study staff right away.

Inconvenience of Study Visits

This trial will require a hospitalization after the initial dose and multiple study visits thereafter. The time commitment, interactions with the hospital system, and travel to and from visits may be a burden on you and your study partner.

Risk of exclusion from other trials

Many clinical trials specifically exclude individuals who have recently taken part in previous clinical trials. There exists a risk that a clinical trial for another potential drug for prion disease will open recruitment in the future, and that you will be ineligible to participate because you already participated in this study.

Risks of Cognitive Testing

The neurocognitive tests that will be administered to assess mental performance may be stressful and at times may cause anxiety, fatigue, and frustration. However, most people find these types of assessments to be very tolerable. Testing will be stopped immediately upon your request if you are uncomfortable or unwilling to continue at any time.

Risks of Questionnaires

Questionnaires used in this study may cause you to feel sad or upset. Study personnel are experienced with such evaluations and sensitive to these issues; you are also free to cease or pause participation at any time.

Genetic Information Risks

At screening, your DNA will be used to perform genetic testing for the *PRNP* gene, which determines susceptibility to prion disease. This test is essential for determining eligibility for this study and results may be part of your medical record. Further studies on your DNA will be conducted as part of the research associated with this study; those results will not be disclosed to you or placed in your medical record because there is no treatment or medical importance at this time. While your genetic data will be kept confidential, there exists a risk that it could influence insurance companies and/or employers regarding your health. Learning your genetic results may also have an impact on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk.

Data Security Risks

Your study data will be stored within a database hosted by the University of Iowa or on paper. Only study staff will have access to both these electronic records and paper records. General identifiable information such as your name, date of birth, and contact information (i.e. phone number, email) will be collected and saved within your study records. You will be given a unique study ID and any data sent to outside collaborators will not contain any identifiable information. As such, it will be virtually impossible to link any of these samples back to you.

Risks of Videoconferencing

If meeting virtually via Zoom or Microsoft Teams, study staff will provide you with information on how to access the video conferencing platform. We will launch the video conferencing in a private and secure area. To protect your privacy we ask that you do not take screenshots, photographs, or recordings of any kind with any electronic equipment.

We would like to remind you that a video meeting is similar to us visiting you at home. We may learn more about your home and the people living with you than we would during a visit at the hospital. For example, we may learn information from you that must be reported to public health or public safety authorities. We are required by law to report known or suspected child or elder abuse. If we make such report, the public health and safety authorities can use the information as they see fit and may end up sharing it with other government agencies. Please ask the research staff if you have any questions about this prior to your video visit.

Risks of an Incidental Finding

We are doing this research study to answer research questions, not to give you medical care. The information created by this study will not usually become part of your hospital record. Some tests and assessments performed in this study are not the same as ones that your doctor would order. They may or may not show problems that would be found on a clinical test. However, if we do see something that looks like a medical problem, we will tell you and help you get follow-up care for the problem. If we think that you might have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Confidentiality Risks

Every possible effort will be made to keep the research information strictly confidential, but we cannot provide an absolute guarantee that unintentional disclosure may not occur. However, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Other Risks

Reviewing health-related information might be stressful or make you feel uncomfortable. We will do our best to make you feel as comfortable as possible at all times during the study.

What other treatments or procedures are available for my condition?

There are currently no FDA approved treatments for prion disease. Some individuals may seek palliative care, when appropriate.

Can you still get medical care within [CSS Site] if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get from us now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out before you finish the study. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Review of medical records from hospital admissions or emergency department visits

[CSS Site] has an electronic system that lets your study doctors know if you are admitted to a [CSS Site], or if you visit a [CSS Site] Emergency Department. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs).

No human has ever received PrP-siRNA to date. This is a first in human clinical trial.

Biomarker Samples/ Storing

Your biomarker samples may be studied for genetic material (instructions for cells to work that is in the form of DNA and RNA), proteins or parts of proteins (a part of all cells), and/or other molecules of cell metabolism (e.g. sugars and fats). The Vallabh/Minikel Laboratory located at the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard will store the samples in a secure storage space with measures to protect confidentiality. The samples and data may be analyzed and used by the Vallabh/Minikel Laboratory or their collaborators, such as other researchers or companies working with this lab, while research continues, but no longer than 20 years from the end of this study. Your samples and related data will be used by the Vallabh/Minikel Laboratory or their collaborators for research related to various diseases and conditions. Your samples will not be sold to other people or companies. Results from biomarker

research cannot be used to make decisions about health or medical conditions of you or your family. Biomarker research results will not be made available to you, any insurance company, your employer, your family, or any physician who treats you in the future.

We may also perform a whole genome analysis on your DNA sample. Usually, researchers study just a few areas of your genetic code that are linked to a disease or condition. In whole genome analyses, all or most of your genes are looked at and used by researchers to study links many diseases and conditions.

In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

Research using your samples and whole genome information is important for the study of virtually all diseases and conditions. Therefore, the sample/data banks will provide study data for researchers working on any disease.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop undergoing lumbar punctures
- You can't make the required study visits
- The Sponsor decides to stop the study
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study.

What are the possible benefits from being in this research study?

There are currently no human data supporting any benefits to you individually from taking part in this research study. The main benefit is the opportunity to contribute to research and produce generalizable knowledge about PrP-siRNA and about prion disease.

Will you be paid to take part in this research study?

You will not receive any payment for taking part in this research study. We will reimburse the actual costs of your transportation (including parking), meals, and other approved travel-related expenses incurred for study visits, up to a total of $500.00 per visit. Under special circumstances (such as when special events cause high hotel and flight prices), you may request prior approval for up to $1,500.00 per visit. In any case, reimbursement will be based on actual expenses incurred and may require submission of receipts or other supporting documentation. If you are traveling a long distance for study visits, the study team may use an outside travel vendor (Great Getaways) to help arrange transportation and/or lodging.

Biospecimens collected during this research may be used for collaborative research with for-profit companies. Any profits generated as a result of this research will not be shared with participants. We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples/information are used for this purpose.

What will you have to pay for if you take part in this research study?

The Broad Institute of MIT and Harvard is providing the study drug at no cost. Study funds will pay for the drug and for certain study-related items and services that are done solely for research. However, we may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, with someone in we will arrange for you to speak with someone in [CSS Site] Patient Financial Services about these costs.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

For what type of research will your data and/or samples be used?

Your data and samples from this study will be used mainly to evaluate the safety and tolerability of the investigational drug, as well as to understand molecular markers of prion disease progression. The long-term goals of the research are to learn how to better understand, prevent, diagnose or treat prion disease. Additional future research will be performed using the data and samples that you contribute to this research study. It is not possible to list every research project. Also, we cannot predict all of the research questions that will be important over the coming years. As we learn more, there are new research questions and new types of research may be done.

De-identified samples, such as CSF and blood, as well as data, will also be shared with qualified investigators for additional molecular characterization and research purposes, including but not limited to studies of prion disease. These investigators may include researchers working at other U.S. hospitals or research institutions, as well as researchers outside the United States and/or at for-profit institutions. Your samples and data will not be sold for profit. Research on your samples and data may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens. We also plan to share data and samples with public repositories which anyone can access and from which anyone can obtain data and/or samples. The data and/or samples that will be shared will not have information that could identify you.

Future Contact

After the study ends, we may continue to contact you in order to collect vital status and medical information. You may be contacted every 4 months for the rest of your life, or until you tell the study team not to contact you again for follow-up related to this study, or until we decide to stop contacting you.

Future Access to Medical Records

We would like to be able to access your medical records in the future to evaluate how the study intervention has affected your medical course.

If you take part in this research study, how will we protect your privacy?

Federal law requires Mass General Brigham to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why they may need to do so:

- Mass General Brigham researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Mass General Brigham who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)

- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- If you are travelling a long distance to attend study visits, your name may be given to an outside travel agency, Great Getaways, for the purpose of booking flight, train, or hotel accommodations for travel to and from the study site.
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- The Vallabh/Minikel Laboratory at the Broad Institute.

Some people or groups who get your identifiable information might not have to follow the same privacy rules that we follow and might use or share your identifiable information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your identifiable information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your identifiable information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your identifiable information for any mailing or marketing list. However, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Your samples and data will be destroyed no later than 20 years from the end of this study. Because this study is still ongoing, we cannot give you an exact date when this will occur. Your permission to use and share your identifiable information does not expire.

The results of this research study may be published in a medical book or journal or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate, unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Your Privacy Rights

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

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Participant:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

_____
Print Name

_____ _____ _____
Participant Date Time (optional)

Signature of Guardian or Authorized Representative for Adult:

I give my consent for the person I am authorized to represent to take part in this research study and agree to allow his/her identifiable information to be used and shared as described above.

_____

Print Name (check applicable box below)

- ☐ Court-appointed Guardian
- ☐ Health Care Proxy
- ☐ Durable Power of Attorney
- ☐ Family Member/Next-of-Kin

_____	_____	_____
Signature	Date	Time (optional)

Relationship to Participant:_____

Assent

Statement of Person Giving Assent

- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions, and my questions have been answered.

Signature of Adult:

I agree to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

_____

Print Name

_____ _____ _____

Signature of Adult Date Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study participant.
- I have answered all questions about this research study to the best of my ability.

_____

Print Name

_____ _____ _____

Study Doctor or Person Obtaining Consent Date Time (optional)

Witness to Consent of Participants Who Cannot Read or Write or are Physically Unable to Talk or Write

Statement of Witness

I represent that the consent form was presented orally to the participant in the participant's own language, that the participant was given the opportunity to ask questions, and that the participant has indicated his/her consent and authorization for participation by (check one box as applicable):

☐ Making his/her mark above

☐ Other means _____
(fill in above)

_____	_____	_____
Witness	Date	Time (optional)

Consent Form Version: 4.0
Consent Form Version Date: 08/07/2026

APPENDIX

Study Visits and Duration

Visit Name	Location*	Time since previous visit (Approximate)	Visit Duration (Approximate Hours)
Visit 1 (Screening)		N/A	4 – 5 hours
Visit 2 (Drug administration)		1 week	24 hours
Visit 3 (week 1 post-dose)		1 week	4 – 5 hours
Visit 4 (week 2 post-dose)		1 week	4 – 5 hours
Visit 5 (week 4 post-dose)		2 weeks	7 – 8 hours
Visit 6 (week 8 post-dose)		4 weeks	7 – 8 hours
Visit 7 (week 12 post-dose)		4 weeks	7 – 8 hours
Visit 8 (week 24 post-dose)		12 weeks	7 – 8 hours

[CSS Site] Location*

Study Activities, Duration, and Timing

Assessment/Questionnaire/Procedure and Description	Estimated time in minutes	Visits at which study activity is done
Written informed consent	20 mins	Visit 1
Inclusion/exclusion review	15 mins	Visit 1
Demographics	5 mins	Visit 1
Neurocognitive & Medical History	15 mins	Visit 1
Vital signs	10 mins.	All visits
Physical Examination/Review of Systems, Neurological Exam/Prion Disease Checklist	10 mins	All visits
Adverse Event Review	10 mins	All visits
Concomitant Medication Review	10 mins	All visits
Columbia-Suicide Severity Rating Scale	10 mins	Visits 1, 3-8

Clinical Safety Labs	10 mins	All visits
12-lead ECG	10 mins	Visits 1, 2
TCRC Admission	24 hours	Visit 2
CSF Collection	20 mins	Visits 2, 5, 6, 7, 8
Brain MRI or CT Scan	30 mins	Visits 1, 6
Blood Biomarker Collection	5 mins	Visits 2, 5, 6, 7, 8
DNA Collection	5 mins	Visit 2
MRC-PDRS	10 mins	Visits 1, 2, 5, 6, 7, 8
Cognitive / Behavioral / Functional Assessment	30 mins	Visits 1, 2, 5, 6, 7, 8
Administer Investigational Drug	1 hour	Visit 2
Exit Questionnaire	20 mins	Visit 8