UNIVERSITY OF PENNSYLVANIA
RESEARCH PARTICIPANT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamics of Intrathecally Administered ALN-APP in Patients with Cerebral Amyloid Angiopathy (CAA)
Principal Investigator:	Aaron Rothstein, MD 3400 Spruce Street, 3 West Gates Building Philadelphia, PA 19104 215-662-3339
Emergency Contact:	Stroke on-call physicians 215-349-5990
Sponsor	Alnylam Pharmaceuticals, Inc.

Research Study Summary for Potential Participants

You are being invited to participate in a research study. Your participation is voluntary, and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to test the safety and efficacy of Mivelsiran (ALN-APP) and find out what effects, if any, ALN-APP has on people with Cerebral Amyloid Angiopathy (CAA).

If you agree to join the study, you will be asked to complete the following research procedures: injections of the study medication, Mivelsiran (ALN-APP), or placebo and approximately 10 study visits over 24 months.

Your participation will last for potentially up to 48 months.

It is unknown if Mivelsiran (ALN-APP) will positively impact your CAA, but during this trial you will be closely monitored and receive routine health checks.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you have been diagnosed with Cerebral Amyloid Angiopathy (CAA).

Your doctor may be an investigator in this research study. You do not have to participate in any research study offered by your doctor. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. You may also decide to discuss the study with your family, friends, or family doctor. Being in a research study is different from being a patient. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study.

If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

Alnylam Pharmaceuticals, Inc., along with co-sponsor Regeneron Pharmaceuticals Inc., is sponsoring this research study to test the safety and efficacy of Mivelsiran (ALN-APP) and find out what effects, if any, Mivelsiran (ALN-APP) has on people with Cerebral Amyloid Angiopathy (CAA). CAA is a neurological condition in which amyloid proteins build up in the walls of blood vessels in the brain, causing problems such as bleeding into the brain. The objectives of the study include:

- To evaluate whether Mivelsiran (ALN-APP) decreases the number of brain microbleeds in people with CAA;
- To evaluate whether Mivelsiran (ALN-APP) affects other aspects of CAA, such as symptoms and brain imaging findings; and,
- To evaluate the safety and tolerability of Mivelsiran (ALN-APP) in people with CAA.

In this study, we will be enrolling populations with two different types of CAA: Dutch-type CAA and Sporadic CAA. Changes to a person's genes, specifically in the APP gene, can cause CAA to develop in younger, typically middle-aged people. Dutch-type CAA, seen in people carrying a known gene mutation for Dutch-type CAA, is an example of this. This study itself will not entail genetic testing. Rather, determination of eligibility for the Dutch-type CAA group of patients will be based on the results of individuals' prior genetic testing. CAA can also occur in individuals without APP mutations. This is known as Sporadic CAA and typically occurs in elderly individuals and increases with advancing age.

This study design and requirements are documented in a protocol (instructions for how the study should be run) that everyone working on the trial follows. This protocol and all associated documentation have been reviewed and approved by the relevant ethics committee.

Mivelsiran (ALN-APP) is considered to be “investigational”, meaning it is not currently approved by regulatory authorities for the treatment of CAA. Mivelsiran (ALN-APP), by reducing the production of amyloid precursor protein (APP), may reduce the unwanted build-up of a protein, called β-amyloid, in the walls of blood vessels in your brain. The ALN-APP-002 study wants to understand whether this reduction, if it occurs, will impact the progression of CAA, for example by reducing the amount of bleeding in the brain.

In this document, the term “Study Drug” refers to either the investigational medication or placebo. A placebo is an inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested. In this trial, the effects of the active drug are compared to the effects of the placebo. Throughout the trial, the Study Drug will be administered through an injection into the fluid around your spinal cord (intrathecally) by a procedure called a lumbar puncture (also known as spinal tap) by the study physician or by a clinician designated by the study physician.

How long will I be in the study?

Your participation in this study is expected to last for at least 30 months, with the option to extend up to 48 months.

What are the Conditions for Participating?

Participating in this study is voluntary. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Neither will it impact the ordinary healthcare treatment you are receiving.

If you wish to take part, you must:

- Agree to provide your study doctor with your medical records and alert them if you start a new medication or dietary supplement, including vitamins and minerals, herbal medications, and vaccines (including those for COVID-19) or have any change in your health during the study.
- Attend all appointments and receive all study drug administrations.
- Complete all study assessments.
- Report all side effects that you experience during the study to your study team.
- Allow your study doctor to continue to review your medical records or public records to understand the status of your health after the study ends (or after your participation in the study ends).
- Consent to the collection, processing, and storage of your samples.

What can I not do?

- You must not take part in another clinical research study while you are participating.

- You or your partner must not get pregnant because effects on a fetus are currently unknown. Contraception details are included in Section 4.2.
- You and anyone in your immediate support network must not share information from or about the trial with other participants, on social media, or in the public domain. This is to avoid biasing how others may feel about, and behave in, the study and ensures that the trial results will be considered valid by regulatory authorities.
- You must abstain from strenuous exercise for 48 hours prior to each blood and/or CSF collection.

What am I being asked to do?

Your participation in this study is expected to last for at least 30 months, with the option to extend up to 48 months. After signing the informed consent form, you will have some tests to determine if you meet the study requirements. If the screening tests confirm you meet the study requirements, you may enter the study, which will consist of the **Double-Blind Treatment Period** followed by the optional **Open Label Extension.**

During the **Double-Blind Treatment Period** you will be randomly assigned to receive an injection into the fluid around your spinal cord of Mivelsiran (ALN-APP) or placebo. The term “double-blind” means that neither you nor the study doctor will know if you receive Mivelsiran (ALN-APP) or placebo during this part of the study. Participants who choose to participate in the **Open-Label Extension,** after the end of the Double-Blind Treatment Period, will all receive Mivelsiran (ALN-APP).
This study is expected to include approximately 200 participants. Below is an overview of what to expect if you participate in the study.

Screening: The screening period is expected to take 1-3 study visits and can last up to 2 months. Screening activities, such as clinical evaluation, blood tests, and brain and spine imaging, will take place at the study site and affiliated diagnostic testing centers, and the results of these activities will be used to see if you qualify for the study. If other treatment options are available, these will be discussed (also see later in this form)

Double-Blind Treatment Period: This part of the trial includes approximately 10 study visits over 24 months.
Generally, you will go to the clinic where you will meet with your study healthcare team and affiliated diagnostic centers. They will ask how you have been and perform tests that include:

- Collecting blood, urine, and cerebrospinal fluid samples
- Measuring your blood pressure, height and weight
- Questionnaires and cognitive assessments
- Magnetic resonance imaging (MRI) scans of the brain (at select visits)

The total amount of blood taken at each visit is about 3mL to 55mL (less than 1 teaspoon to about 11 teaspoons). Across the Double-Blind period, this adds up to

about 13 ounces(377mL) (1.5 cups which is roughly 83% of the volume taken in a single blood donation). If you consent to optional samples for future research, an additional 6mLs will be collected.
You will also receive the study drug at some appointments.
You may have the option to conduct certain study visits at your home with a home health nurse, or via telemedicine (e.g., video call with the study doctor). For more information on this service, please see section 5.9. Please talk to your study doctor to learn if it is an option for you.
Potential benefits: It is unknown if Mivelsiran (ALN-APP) will positively impact your CAA, but during this trial you will be closely monitored and receive routine health checks.
Potential risks: There are potential side effects, such as reaction to the Mivelsiran (ALN-APP) or to study procedures such as the lumbar puncture as described in this consent. Your study doctor will discuss risks in detail with you. For more information on risks related to this study and Mivelsiran (ALN-APP) see the Risk Section.

Open Label Extension Period: This part of the trial includes approximately 5 study visits over 18 months. Study activities that were performed in the Double-Blind Treatment Period will continue during this part of the trial. Generally, you will go to the clinic where you will meet with your study healthcare team and affiliated diagnostic centers. They will ask how you have been and perform tests that include:

- Collecting blood, urine, and cerebrospinal fluid samples
- Measuring your blood pressure, height and weight
- Questionnaires and cognitive assessments
- Magnetic resonance imaging (MRI) scans of the brain (at select visits)

The total amount of blood taken at each visit is about 32mL to 37mL (about 6.5teaspoons to 7.5 teaspoons). Across the Open-Label Period, this adds up to about 5.6 ounces (196mL) (less than one cup (0.7) which is roughly one third of the volume taken in a single blood donation).

In this Open Label Extension portion of the trial, you will also receive Mivelsiran (ALN-APP) at some appointments.

Follow up: There will be 1 additional safety visit 12 months after the last study drug dose, whether or not you participate in the Open Label Extension.

List of study procedures

Study Procedure		Frequency	Main risks
Cognitive Assessments and Questionnaires	You will be asked to complete cognitive measures to assess your functioning and	Most	

	memory as well as questionnaires about CAA and how it impacts your daily activities, quality of life and mental health status.		
Electrocardiogram (ECG)	Sticky pads will be placed on your chest, arms, and legs. The pads are connected by wires to a machine that checks the rhythm and activity of your heart.	Most	You may develop minor skin irritation from the sticky pads that are placed for the ECG.
Magnetic Resonance Imaging (MRI)	This test uses radio waves, magnets, and a computer to take pictures of your brain. Additionally, while receiving the MRI, you will be asked to look at repeating images. The MRI will measure your brain's response to these images.	Some	An MRI examination causes no pain, but you may have difficulty keeping still or may become nervous in the scanner. The sound of the MRI scanner can be quite loud; you may be given special ear plugs to minimize the noise.
Blood and Urine Samples	Samples will be collected to see how your body processes the study medication, monitor how your body is doing overall, such as checking your liver and kidney function, and, if you are female of childbearing potential, check if you are pregnant.	Most	The study doctor will check the skin for reactions around where the needle for blood collection is inserted. There is a small risk of side effects (e.g. redness, pain, bruising, fainting, or infection).

Lumbar Puncture	This procedure is also called a spinal tap. The doctor will numb the area where a needle will be inserted between two bones into your lower spine to remove a sample of cerebrospinal fluid (CSF). CSF is the liquid that is found around your brain and spinal cord. A sample of your CSF will be collected to check how safe and effective the study medication is. You will also receive the study medication via this procedure.	Most	A Lumbar puncture / spinal tap is a relatively safe procedure, common side effects from the spinal tap include: • Headaches in up to 3 out of 10 people which might improve in a laying down position • Nausea, vomiting, dizziness • Bleeding • Infection • Ringing of ears, blurry eyesight • Discomfort or pain in your lower back or back of legs • Numbness, tingling, and muscle weakness around your spine • Lightheadedness or fainting There are a few rare side effects from the spinal tap including bleeding in the brain or non-cancerous tumors that develop under your skin.
X-ray fluroscopy	This is a type of medical imaging that shows a continuous X-ray image on a monitor. The study doctor may decide to use this procedure to identify the correct insertion site during the LP to guide the insertion of the needle. During a fluoroscopy procedure, an X-ray beam is passed through the body and the image is		X-ray fluoroscopy may be needed during the LP to help the clinician place the needle in the right place. Therefore, you will receive a radiation dose. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the

	transmitted to a monitor so the injection site and insertion of the needle can be seen in detail.		doses you will receive, it is very likely that you will see no effects at all.
Optional Samples for Exploratory Analysis (may include exploratory DNA testing)	If you agree, additional blood and residual urine and CSF samples will be used for biomarker testing and for future analysis to learn more about the disease and also how the investigational medication works.	Few	The study doctor will check the skin for reactions around where the needle for blood collection is inserted. There is a small risk of side effects (e.g. redness, pain, bruising, fainting, or infection). The Genetic Information Nondiscrimination Act (GINA) is a federal law designated to protect you from health insurance and employment discrimination based on genetic information. It is illegal for health insurance providers and most employers to ask for genetic information to make decisions about a person's eligibility or coverage or to make employment decisions

Other tests that are routine general health care are not listed here. Please tell your study doctor or nurse immediately if you experience any unusual or undesirable effects.

What are the possible risks or discomforts?

Potential Risks Related to Mivelsiran (ALN-APP)**:** During some studies in animals, there has been data that Mivelsiran (ALN-APP) may lower White Blood Cell (WBC) count at doses higher than planned for this study. During these studies, the WBC count came back to normal after drug administration to animals stopped. Although the study you are participating in does not expect to have any doses where this will occur, WBC monitoring will be done during the course of the study to minimize the risk to your health. Since WBCs are part of the immune system, low WBC levels could increase risk for infection.

In a study of Mivelsiran (ALN-APP) in monkeys, two animals had convulsions lasting up to 3 minutes and a few others had tremors (shaking) of the whole body and/or trouble balancing. Some animals from these groups also had microscopic findings (decrease in the number of cells) in the part of the brain called the cerebellum that controls movement. This has only happened in animals that received multiple injections.
Clinical studies that looked at a different class of drug (BACE inhibitors) showed some worsening in cognition that was associated with treatment. This class of drugs (BACE inhibitors) did lower one type of APP protein, but through a different mechanism than the study drug. The evidence so far suggests that the study drug mechanism would not be expected to cause a similar effect of cognitive worsening. Nevertheless, the Sponsor has established a frequent schedule of cognitive assessments in this study to monitor the status of participants.

If significant new safety information emerges during the course of the clinical studies with Mivelsiran (ALN-APP) that might affect your willingness to participate, your study doctor will inform you as soon as possible.

It is possible some patients could have side effects to Mivelsiran (ALN-APP) that we do not know about yet. If you have a severe side effect, the study doctor may ask you to not continue in the study.

Allergic reactions
Like any pharmaceutical product, there is a chance that you may experience an allergic reaction. Symptoms of an allergic reaction may include hives, rash, itching, flushing, swelling of the lips, tongue or throat, sudden shortness of breath, decreased consciousness, nausea, vomiting, and decrease in blood pressure. Severe allergic reactions (also known as anaphylaxis) can be life threatening and may require emergency treatment or hospitalization. If you think you may be having an allergic reaction to ALN-APP immediately seek medical attention and contact the study doctor or his/her study staff.

ARE THERE ANY RISKS WITH USING MIVELSIRAN (ALN-APP) IN COMBINATION WITH OTHER MEDICINES?
The side effects of using Mivelsiran (ALN-APP) in combination with other medicines are not known at this time. It is very important to tell your study doctor or his/her study staff about any medicines you are taking, discuss any dose changes before they happen, any medicines you have taken in the past and any medicines you may start taking while in the study. This includes medicines prescribed by another healthcare provider, as well as those obtained without a prescription (over the counter medications or supplements). Medicines that you take that require their levels to be followed may need to have their levels checked more frequently while you are on the study.

What risks are there if I am pregnant, breastfeeding, or plan to become pregnant while taking Mivelsiran (ALN-APP)?

In addition to the risks described**,** there may be risks that are currently unknown and not foreseeable. For example, it is not known if Mivelsiran ALN-APP might harm an unborn baby or breastfeeding child. If you are female and able to become pregnant, it is important to:

- Stop breastfeeding once you have your first dose of study medication until 12 weeks after your dose of study medication.
- Use acceptable means of contraception (ways to help prevent becoming pregnant):
  - starting at 30 days before receiving your first dose of study medication
  - continues until approximately 25 weeks or 180 days after your last dose of study medication or until study completion, whichever is longer

Be sure to review acceptable means of contraception with your study doctor.
Risks to unborn babies/infants will be minimized by excluding women who are breastfeeding from clinical studies. To further minimize any potential risk, if you are a female patient of child-bearing potential you will have a pregnancy test performed at screening and must test negative for to participate in the study. Pregnancy tests will also be given regularly throughout your study participation.

If you are a male participant, contraceptive measures (e.g., a condom) are required during sexual intercourse with female partners of child-bearing potential, including partners that are already pregnant, throughout your study participation and for 180 days after the administration of study drug or until study completion, whichever is longer. No one method of contraception is 100% effective.

You should avoid ova or sperm donation for 180 days after administration of study drug or study completion, whichever is longer. If your partner becomes pregnant during your participation in this study or in 180 days after your last dose of study drug, inform your study doctor immediately. With your partner`s permission, the study doctor will collect information on her pregnancy and its outcome.

By participating in this study, we may discover health conditions that you were not previously aware of. Before participating you should consider if this will affect any insurance you have and seek advice if necessary.

In laboratory studies, there was no evidence that the study drug is genotoxic; however, long-term studies regarding carcinogenicity and teratogenicity have not been completed, and there may be potential risks to subjects or to the embryo or fetus that are unforeseeable.

MRI risks:

What is an MRI?

MRI (Magnetic Resonance Imaging) MRI is a type of scan that uses radio waves to take detailed pictures of the body. You will be asked to lie on an MRI table where the technologist will place a receiver on the part of your body to be studied. You will be

provided a blanket for comfort and earplugs since the MRI makes noises while it is scanning. You will still be able to hear some sound to ensure you can communicate with the technologist and can follow any direction given throughout the MRI scan. The technologist will slowly slide you into the MRI magnet where radio waves will be transmitted into you.

Screening for MRI:
You must complete a screening evaluation form in advance of the MRI exam for the presence of medical implants or other foreign bodies that could pose an injury when undergoing MRI. The screening is only as effective as the provided medical history. In cases where there is insufficient information to evaluate the risks associated with an implant or foreign body, the MRI study will not be allowed to proceed.

Flying Objects
The greatest risk of MRI is a magnetic object flying through the air toward the magnet and hitting you. To reduce this risk, we require that all people involved with the study remove all magnetic metal from their clothing and all magnetic metal objects from their pockets. No magnetic metal objects are allowed to be brought into the magnet room at any time except by approved personnel. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the room.
Medical Implants and

Foreign Bodies
There is a potential risk of MRI for subjects with medical implants or other metallic objects in their body. All subjects undergoing MRI scanning must complete a screening evaluation risk in advance of the study for the presence of medical implants or other foreign bodies that could pose an injury. Every effort will be made to insure that disclosed implants or foreign bodies do not pose a risk to subjects. In cases where there is insufficient information to evaluate the risks associated with an implant or foreign body, the MRI study will not be allowed to proceed.

Possible side effects related to the MRI scan include:

Possible:

- Anxiety/stress
- Claustrophobia
- Discomfort
- Nausea/vomiting
- Tingling in arms

Rare, but serious:

• Injury related to the presence of metallic or surgical implants or metal pieces in the body and the MR magnet. This also includes: wearable sensors, medicinal patches, certain types of tattoos, and hair weaves containing metallic threads. It is important that you let the MRI team know about whether you have these before the MRI procedure. .

This MRI is not a clinical scan. It is possible that during the course of the research study, the Investigator may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you inform you if the finding requires any further action on your part. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

Risks of Genetic Testing

If you agree to the collection of an additional blood sample for future research, this research may include exploratory DNA testing. Participation in this additional research is optional. You do not have to consent to this to participate in the Main study. This research may include genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

It is unknown if Mivelsiran (ALN-APP) will help improve your CAA and you may receive no direct benefit from your participation, but the information we get from this study may help others with the same condition in the future. You will receive study-required procedures at no cost to you regardless of whether you get Mivelsiran (ALN-APP) or a placebo for the first part of the study, you will also still receive currently available standard healthcare support throughout participation.

You may not get any benefit from being in this research study.

What other choices do I have if I do not participate?

You do not need to participate in this study to receive treatment for your condition. Your study doctor can talk to you about what other treatments are available. These treatments may include symptomatic treatments.

Will I be paid for being in this study?

You will be eligible to receive reimbursement for reasonable travel costs and effort required by you to participate in the study.

The Sponsor is working with Greenphire, LLC, who may assist you with Patient Support Services while you participate in the study, which can include travel, payments and other customized services (depending on your needs). If you decide not to use these services, it will not impact your participation in the study and the site staff will assist you using other means. If you are interested in utilizing Greenphire support services, let your study coordinator know, and they will provide you with additional information and a separate consent form including data privacy language for you to read and sign.

Will I have to pay for anything?

Medical Costs: The Sponsor will pay for the Study Drug, tests and procedures needed in this study. You/your insurance company continue to pay for your standard medical care. You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

What happens if I am injured from being in the study?

If you take part in this study you will be given a card for your wallet that tells you what to do if you feel ill or have an emergency during this study. Always tell the doctors and nurses looking after you that you are taking part in the study.

- **If you need immediate assistance:** go to your nearest Emergency Room for treatment or call 9-1-1.
- **If you feel unwell or have concerns:** immediately contact the study doctor who will treat you or refer you for treatment as required. Our on-call phone number to reach a physician is 215-349-5990.

If you are injured as a result of participating in this study, the Sponsor will cover reasonable costs of treatment for study-related health issues that are not covered by your health insurance or national healthcare systems. The Sponsor will not cover usual medical care or consequences of the natural course of an underlying or pre-existing condition. Signing this form does not stop you from pursuing legal action for the injury. Providing medical care in the event you are injured in the study does not imply any fault or wrongdoing on the part of the Sponsor, your study doctor, or the study center.

<u>What happens if I become pregnant?</u>
If you consent to it, information about your health, pregnancy and fetus will be collected throughout your pregnancy and delivery. Examples of information include ultrasound or imaging reports, discharge summaries, and results of laboratory testing. If you agree to provide information, your involvement will last throughout your pregnancy and delivery. You will not be asked to undergo any additional tests other than those that your health care provider would normally perform in taking care of your pregnancy and your fetus.

The purpose of collecting information on your pregnancy is to learn more about how Mivelsiran (ALN-APP) affects pregnancy. You may provide this information yourself or give permission to your health care provider to release it directly to the study doctor. This is voluntary, and you may decide not to provide any information on your pregnancy, fetus or pregnancy outcome.

When is the Study over? Can I leave the Study before it ends?

You may stop participating in the study at any time without penalty or loss of benefits to which you are otherwise entitled. By stopping, you will:

- No longer receive the Study Drug
- Not be able to re-enroll in the study, even at a different clinic
- Be asked to visit and/or call the study clinic for a final follow-up assessment to see how you've been after stopping

The study doctor may contact you or your primary doctor to ask about your health after the study is over. Other individuals such as a family member or caregiver will not be contacted without appropriate permission.

The data collected about you (including data that can identify you (your "Personal Data") and data that does not directly identify you but links you to a randomly generated code (your "Coded Personal Data") and samples remain part of the study database and may continue to be used as described in this consent form.

Can I be forced to stop participating in the Trial?

You may also be removed from the study without your permission at any time if:

- You do not follow the study doctor's instructions
- It is found that you should not be in the study – if this happens, the reasons would be discussed with you
- The study is stopped by the Sponsor or a regulatory authority for any reason
- The study or study drug becomes harmful to your health
- The Sponsor completes study enrollment before you enter the treatment period, even if the screening tests confirm you meet study requirements (this is because the Sponsor can only have a limited number of people enroll in the study)

  Your study doctor will discuss other available treatment options.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being

overseen by the Food and Drug Administration (FDA), they may review your research records.

The confidentiality of your information will be protected in the following way during the study: your de-identified and coded data will be stored in a locked office that is only accessible to study team members.

Will information about this study be available to the public?

Within about 12 months after the trial has ended, a summary of the study results will be made available to you. Study results may also be published – in all cases you will not be identifiable from published results. Study results may be published at conferences, in scientific and medical journals, and in the general media.

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

However, you will not be identified in any of these publications or publicly available results.

What may happen to my information and samples collected on this study (e.g. blood, urine, CSF)?

Your samples may be tested or analyzed during and after the study ends and may be shared with other organizations as part of the study (as described below). The samples will be stored for up to 10 years (or as required or allowed by local law) after the end of the study, and then they will be destroyed.

If consented to, the Sponsor may use the Coded Personal Data or designated biological samples for future or additional research projects during or after the study. If you consented to future research, you may withdraw that consent, and your samples will not be used for future research.

You will not be given the results from testing that may be performed on your identifiable specimens as a part of future research.

If you have questions about the storage of your information and samples, or have changed your mind, you can contact Dr. Aaron Rothstein at 215-662-3339.

Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

If you have never received care within Penn Medicine and are participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for you for the purpose of maintaining any information produced from your participation. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). If you have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

What may be placed in the EMR?

Information related to your participation in the research (e.g., laboratory tests, notes from your physician, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by Penn Medicine.

Once placed in your EMR your information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in your care. This information is shared to improve the quality, safety and efficiency of your healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a participant, have access to research related information within the EMR?

The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of your participation in this research, you will have access to research related information within your EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Some information specific to this clinical research study may be shared with you in a delayed manner, shared with you at the end of the study, or not shared with you. Not sharing or delaying certain research information within your EMR may be necessary to protect the integrity of the trial results or for other reasons.

What information about me may be collected, used or shared with others?

Personal Data is any information that may identify you. Examples include: Your name, date of birth, gender, address, phone number, medical condition and medical history, images such as scan results, information from samples, race and ethnicity and genetic data.

Personal Data is collected and kept confidential under the supervision of your study site. Your study site will replace identifiers contained in your Personal Data (such as your name and medical record number) with a randomly generated Participant ID. This ensures that all information shared beyond the study site (including information shared with the Sponsor) becomes “Coded Personal Data”.

Coded Personal Data of study participants may be combined and used to:

- assess the safety and efficacy of the investigational medication,
- submit study results for the investigational medication to health authorities,
- publish the study results, and
- support scientific research.

We have put in place reasonable and appropriate physical, electronic, and administrative safeguards to help protect the privacy of your Personal Data and Coded Personal Data. However, it is impossible to guarantee 100% security for all data collected. People who have access to your Coded Personal Data may be located in other countries. You should be aware that some countries may not offer the same level of privacy protection as you are used to. However, the Sponsor will ensure protection of the Coded Personal Data as required by law during the transfer as well as when it has arrived in the country of destination.

As a pharmaceutical company, the Sponsor has a legal obligation to collect data to be able to make regulatory submissions for the clinical trial and a legitimate interest to process your data as is necessary for scientific research purposes. These are the legal justifications for the collection and processing of your data. In addition, the Sponsor may rely on your consent for specific purposes of the processing of your Personal Data and Coded Personal Data.

No Personal Data will be made public.

Where may my information be stored?

Information related to your participation in clinical research will be contained in a clinical trial management system (CTMS). A clinical trial management system (CTMS) is used to register your information as a participant in a study. This allows for your research data to be entered and stored for the purposes of study operational and financial applications and other activities required as part of the conduct of the research. Once

placed in the CTMS your information may be accessible to other authorized personnel at Penn Medicine that support research operations. Your information may be held in other research databases.

Who at PENN may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of Penn Medicine, might receive my information?

A list of people who will be able to see your Personal Data and Coded Personal Data are in the table below:

Personal Data	Coded Personal Data[1]
Study site doctor and personnel	The Sponsor, their staff, collaborators, and partners (such as researchers, commercial partners, and staff at scientific journals)
People authorized by the Sponsor (e.g. study monitors[2]) who check that data are correct	Insurance companies, as applicable
Vendors (people who work for the Sponsor such as home research nurses)	Vendors (such as contract research organisations [CROs] who help to deliver the study)
Health authorities (government agencies who ensure that clinical studies are conducted to high quality standards)	Health authorities located in different countries around the world
Institutional Review Boards and ethics committees who are responsible for protecting participants' rights	A company looking to purchase the Sponsor or part of its business

[1]Anyone who can see your Personal Data will also be able to see your Coded Personal Data.

[2]Where local regulations allow, a study monitor may have remote access to review study documents. If this happens, it will be done with your study site's permission and in a manner that protects the confidentiality of your data.

Once your personal health information is disclosed to others outside Penn Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to Penn Medicine procedures developed to protect your privacy.

How long may Penn Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

However, Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

If you wish to exercise any rights regarding the Personal Data which is at the study site, you should contact the study site at 215-349-8651. For any queries related to Coded Personal Data, which is collected by the Sponsor, you can contact the Sponsor Data Protection Office at privacy@alnylam.com.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Participant HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research participant?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research participant, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your protected health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that protected health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Confirming understanding:

Confirm you understand and agree to each of the following:

- I have read[1] and understand the information in this document, or someone has read the document to me.
- I have received a copy of this information sheet and consent form to keep for myself
- It is my choice to participate, I do so voluntarily, and I can stop taking part at any time
- My Personal Data, Coded Personal Data, and biological samples will be collected, stored and used as described above.
- I agree to complete the study procedures and follow the study doctor's instructions

Awareness of primary doctor:

I agree that my primary doctor can be told that I am taking part in this clinical research study and can obtain and share medical information:

☐ YES ☐ NO ☐ Not applicable as I **do not** have a primary doctor

Future Research (optional):

I consent to the storage of residual and collection of additional optional biological samples (blood, urine, CSF) during the study to be used and analyzed in combination with my Coded Personal Data in order to conduct future research in CAA

☐YES ☐ NO

I consent to the collection of an additional DNA sample during the study to be used and analyzed in combination with my Coded Personal Data to conduct future research in CAA. Studies will not analyze all of your DNA, only the portions related to CAA and the effect of the treatment with Mivelsiran (ALN-APP).

☐ YES ☐ NO

Printed Name & Signature of Participant	Date of Signature

Printed Name & Signature of impartial witness (if applicable)[1]	Date of Signature

[1]*An impartial witness is a person, independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the participant.*

Home Care Services through Illingworth:

I have reviewed the details of the Illingworth home care services included in this informed consent form and have had a chance to review these details and the procedure with my study doctor. All my questions have been answered. I will make my decision known by either checking the "Yes, I agree" or "No, I do not agree" to participate.

☐ YES, I **agree** to participate in the home care services
☐ NO, I **do not agree** to participate in the home care services

Pregnancy Research (Optional):

I consent to provide information on my pregnancy, fetus and pregnancy outcome. I voluntarily agree that the health care provider(s) caring for my pregnancy and my fetus may disclose to the team treating me for this study, any relevant information in their possession pertaining to my health, pregnancy, fetus and pregnancy outcome.

☐ YES
☐ NO
☐ Not applicable

For completion by the Study Team

- I, the undersigned study personnel, confirm that I have verbally given the necessary information about the study, answered any additional questions, and did not exert any pressure on the participant to participate in the study.
- I declare that I acted in full accordance with the ethical principles described in GCP Guidelines, and other national and international legislation in effect.
- A copy of this consent form(s), signed by both parties, will be provided to the participant.

Printed Name & Signature of Person Obtaining Consent	Date of Signature