ADVANCE

CLINICAL STUDY FOR FARBER DISEASE

A Guide for Patients and Caregivers

Advancing research for people living with Farber disease

About the Study Name

The full name of the ADVANCE study helps explain what the study is researching and how the study will work.

ADVANCE: A Randomized Double-Blind Placebo-Controlled First-In-Human Dose-Escalation Study of the Safety and Efficacy of Intravenous RVT-801 in Pediatric and Adult Patients with Acid Ceramidase Deficiency Presenting as Farber Disease

So What Does That Mean?

Randomized
Study participants will receive the active study medicine, RVT-801, or an inactive placebo by chance. In this study, approximately two-thirds of people who join the study will receive the active study medicine, RVT-801, and one-third will receive the placebo. Once randomized, study participants will receive the same treatment throughout the study, except in very special circumstances. When this study is finished, participants may join a separate extension study which will not be randomized—all participants will receive the active study medicine.

Double-Blind
To make sure doctors or patients cannot change the outcome of the study (bias), no one in the study (patients or families) and no one running the study (doctors or nurses) will know who receives the active study medicine and who receives the inactive placebo.

Placebo
A substance that looks like the study medicine and is given in the same way but does not contain active medicine. In this study, the placebo will be a salt watermixture that is often used by doctors every day and will have no impact on the body. A placebo is used in a randomized, doubleblind study to prevent bias[1].

First-in-Human
When a new medicine is given to peoplein a study for the first time, it is called a first- in-human study. Dose Escalation In a clinical study, doctors may increase the dose of the medicine being studied to understand if the recommended dose is safe, tolerated, and effective.

Safety and Efficacy
Doctors want to figure out if the study medicine is safe and if it addresses the disease symptoms.

Intravenous RVT-801
The study medicine, RVT-801, will be slowly given by infusion through a tiny, flexible plastic tube (cannula) in the arm or where the doctor recommends.

Pediatric and Adult Patients
Children and adults may participate in this study.

Acid Ceramidase Deficiency Presenting
as Farber Disease This is the disease doctors hope to treat. If an enzyme called acid ceramidase is absent or not working well enough, a person may have what is known as acid ceramidase deficiency. The ceramide inside the cells can build up and this can cause Farber disease.

Thank You

Dear Caregivers and People Living with Farber Disease,

This companion guide is for caregivers and people living with Farber disease who are considering the ADVANCE Clinical Study for Farber Disease.

As you review the informed consent document from your doctor, you can refer to this guide to help understand the ADVANCE study, Farber disease, and clinical research. The ADVANCE study team is also available to answer questions. They will lead you through the informed consent process, which means you can ask questions and learn the details about this clinical research study before deciding to join. At any time, you can decide to leave the study. Joining a clinical research study is an important decision that you should discuss with your doctor. You can feel confident in the choice you make for yourself or the child you care for by learning about the disease, how clinical research works, and what to expect with the ADVANCE study.

Thank you for your interest in helping advance research for people living with Farber disease.

Sincerely,

ADVANCE
CLINICAL STUDY FOR FARBER DISEASE

The ADVANCE Study Team

Clinical Research

Clinical Research

Clinical research is a team effort. People who join a study become part of that team. Clinical research is what advances new treatments and gives other people living with the disease hope.

Clinical research studies, also called clinical trials, are how doctors learn if new medicines or new ways of using existing treatments are safe and improve the health of people[2].

There are benefits and risks to joining a clinical research study, and learning about them is part of the informed consent process[3]. A study doctor will review the specific risks and benefits of the ADVANCE study with anyone interested in joining the study.

The best interests and safety of people who participate in clinical research studies are closely monitored. Studies follow an approved plan called a protocol. Institutional Review Boards (IRBs) and Ethics Committees (ECs) must approve protocols to make sure people who participate are safe.

Why do people join clinical studies?

Some people participate in clinical research to help others with their same disease by contributing to medical research and improving the understanding of potential treatments. In some cases, people participate to have access to investigational medicines that could benefit them before they are approved.

Other people choose not to participate in clinical research studies because they aren't comfortable with not knowing if the treatment will work, do not have time for appointments, or because they are not comfortable with the potential health risks that may be involved with joining a study.

ACERAGEN

ADVANCE STUDY SPONSOR

The ADVANCE study is sponsored by Aceragen, a biopharmaceutical company focused on developing transformative therapies for patients living with rare diseases. Aceragen is also developing RVT-802, an investigational therapy for the treatment of a rare disease called complete DiGeorge Anomaly.

ADVANCE study doctors and hospitals are being paid for their time because this is a research study and not part of regular patient care.

Notes

Advanced Study

Why is the Advanced Study Being Done?

The goal of the global ADVANCE Clinical Study for Farber Disease is to understand if the study medicine, RVT-801, may help address Farber disease symptoms. This study is for children and adults who have been diagnosed with Farber disease by a physician.

RVT-801: Study Medicine

The ADVANCE clinical study will help doctors understand if the study medicine, which is called RVT-801, can help treat Farber disease by replacing the enzyme that is absent or doesn't work well enough in people with the disease.

The ADVANCE study is a randomized study, which means study participants will receive the active study medicine, RVT-801, or an inactive placebo by chance. In this study, two-thirds of participants will receive the active study medicine and one-third will receive the placebo. When this study is finished, participants may join a separate extension study which will not be randomized—all participants will receive the active study medicine.

People living with Farber disease have an acid ceramidase enzyme that is absent or doesn't work well enough[4,5]. RVT-801 is a recombinant (or made in a lab) form of human acid ceramidase. RVT-801 will be given slowly by infusion through a tiny, flexible plastic tube (cannula) placed in a blood vessel, which can take more than three hours.

Doctors hope RVT-801 can reduce the amount of ceramide in the body and address Farber disease symptoms. For example, the ADVANCE study doctors will be looking to see if the size and number of bumps (nodules) under the skin decrease.

There are risks and benefits to participating in a clinical study and receiving an experimental medicine. The study team will explain the risks and benefits. If you still have questions or do not understand the study, please speak to a member of the ADVANCE study team.

Advanced Study Questions

How long is the ADVANCE study?

The ADVANCE study will last about 7 months (28 weeks). Throughout the study, the study doctor will carefully monitor the health and disease symptoms of everyone in the study.

There will be approximately 15 visits (about every two weeks) to the study doctor. Each visit will include many examinations and tests that may take two days. Before certain visits, your doctor may ask you to not eat or drink anything the morning before your appointment. If you are worried about this, tell your study team and they can make other plans if needed.

How many people are participating in the ADVANCE study?

The ADVANCE study team members around the world will enroll 12-15 people in the study.

What if the symptoms related to Farber disease become worse or life-threatening during the study?

If the study doctor believes the disease symptoms are becoming worse, requiring hospitalization or are life-threatening, there are several options the doctor may recommend:

1. Leave the study.
2. Reveal if the study participant is currently on placebo or active study medicine.
   - If on placebo, take the active study medicine for the rest of the study.
   - If on active study medicine, increase the amount of the active study medicine received for the rest of the study.

When the study is over, can study participants continue to take the study medicine?

At the end of the ADVANCE study, participants may choose whether to participate in an extension study of the same active medicine (RVT-801). In this study, there will be no placebo—everyone participating in the extension study will receive the active study medicine, RVT-801, and will continue to be monitored by the study team.

There will be an opportunity to to ask additional questions about the extension study. The study doctor will explain the potential risks and benefits, including how personal information may be used.

Notes

Farber Disease

What Causes Farber Disease

Farber disease is an inherited or genetic disease which is caused by mutations in the *ASAH1* gene. When there's a problem with this gene, the body produces a defective version of an enzyme called acid ceramidase that is absent or doesn't work well. This disease is also known as acid ceramidase deficiency[6,7].

Mutations in the *ASAHI* Gene ▶ **Enzyme (Acid Ceramindase) Deficiency** ▶ **Farber Disease**

Mutations in the *ASAH1* Gene

Genes are inherited from our parents and give instructions to our cells. If the genes have mutations, the instructions may not work right, which can cause a genetic disease[8].

Mutations in the *ASAH1* gene causes the body to produce acid ceramidase enzyme that doesn't work like it should[9].

Enzyme (Acid Ceramidase) Deficiency

People whose enzymes do not work well have acid ceramidase deficiency.

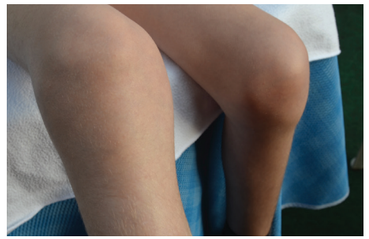
The acid ceramidase enzyme helps break down a lipid (fat), called ceramide, inside the cells. When there is too much ceramide stored in the body, Farber disease symptoms appear.

Farber Disease

- Farber disease is part of a group of genetic diseases called lysosomal storage disorders.
- Lysosomes contain enzymes that help cells grow and reproduce. Some enzymes, like acid ceramidase, help break down and recycle molecules and lipids (like ceramide) that are inside each cell of the body.
- If an enzyme doesn't work well enough, the ceramide inside the cells can build up and cause problems[10].

Farber Disease Symptoms and Severity Vary

As you may know, the most common Farber disease symptoms are painful and swollen joints, bumps (nodules) under the skin, and a hoarse or weak voice. These and other symptoms may appear over time and can vary in how bad they are and how quickly they progress, making it difficult to diagnose and treat[11,12].



Current Treatment Options

There are currently no treatments specific to Farber disease. The only treatments available may temporarily address some of the symptoms, but don't prevent the disease from getting worse[13]. The ADVANCE clinical study will help doctors understand if the new study medicine may help people living with Farber disease.

Notes

What to Expect

What Happens at Each Study Visit?

At the first study visit, you will be asked to read and sign the informed consent document which explains the study details. **By signing the informed consent document, you (1) are saying you understand what will happen to you or the child you care for during the study and (2) are giving your approval to undergo study tests**. Even after signing the informed consent document, you or the child you care for may decide to leave the study at any time.

What to Expect at *Most* Visits

All of the ADVANCE study visits the study doctor will want to know how you or the child you are caring for is feeling and if there are any updates or changes. Below are some of the activities and tests that will happen at most of the visits.

Study Activity	Description	Possible Risks
Medical history/updates	• Share medical information • Provide health, prescription updates	• Minimal privacy risk (medical information will be handled with strict confidentiality)
Lots of questions/questionnaire	• Questions about overall health, nodules (bumps), and impact on daily activities	• Some uncomfortable questions
Check vital signs	• Temperature, heart rate, lungs, blood pressure checks	• Very little discomfort
Infusion	• Study medicine (or placebo) dripped slowly (~3 1/2 hours) through flexible plastic tube into arm or where the doctor recommends	• Risks of receiving RVT-801 are unknown, but may include • Allerigic reaction (rash, feel unwell) • Development of antibodies • Body temperature change • Heart rate increase
Physical Exam	• Height, weight, overall health measure	• None
Blood samples	• Taken for safety, biomarker, antibody testing	• Faintness • Redness, pain, bruising, bleeding from needlestick • Slight infection risk
Don't eat of drink before the appointment	• May be required before giving blood sample • Share any concerns with study team	• Dizziness • Faintness

What to Expect at *Some* Visits

Some study visits may include other tests to see if there are any changes since you or the child you care for started receiving the study medicine or placebo. Your study doctor may ask you to go to another medical center for some of the tests. Your study doctor will let you know what is needed.

Study Activity	Description	Possible Risks
Nodule exam	• Photos, measurements of nodules (bumps) taken to track size	• Privacy minimally at risk because identification might be possible from a feature in photos (photos will not include names)
Walk test	• Walk for 2-6 minutes • Wear sensor on finger to measure heart beats, oxygen level	• Shortness of breath • Tiredness • Pain in joints of nodules
Hand movement test	• Put pegs into holes in a board • Measure hand and finger movements	• Pain in joints of nodules
Breathing test	• breathe in and out of a tube • Measure air moving in and out of lungs	• Shortness of breath • Dizziness
Ultrasound	• Painless way to measure size of liver, spleen	• Very little discomfort • Gel used on skin may feel cold at first
Electrocardiogram (ECG)	• Painless test to measure heart beats • Small stickers will hold wires on chest, arms, legs	• Very little discomfort • Stickers may pull the skin a bit when taken off
Pregnancy test (for some)	• Urine test for girls, women who are old enough to have children	• None

What to Expect at the Final Study

If you or the child you care for decide not to join the extension study or wish to leave the ADVANCE study before it is finished, you will be asked to return for a final follow-up visit. During this appointment, some of the tests will be repeated.

Notes

What to Expect at Advance Study Visits

During your study visits, fill in the ☑ as you go!

(Please note: This is not an official tracking document for the study. It is for study participant or caregiver use only.)

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Final
Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	
What to Expect at Most Visits																
Medical history/ updates	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△
Lots of questions	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△
Check vital signs	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△
Infusion	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△
Physical exam/ weight taken	△	△	△		△		△		△		△		△		△	△
Blood samples	△	△	△		△		△		△		△				△	△
Don't eaet or drink before visit	△	△	△		△		△		△		△				△	△
What to Expect at Some Visits																
Nodule Exam	△	△					△				△				△	
Walking test	△						△				△				△	
Hand movement test	△						△				△				△	
Breathing test	△						△				△				△	
Ultrasound	△														△	
Movement test	△						△				△				△	
Electro-cardiogram (ECG)	△	△													△	
Pregnancy test (for some)	△						△								△	△

Frequently Asked Questions

Frequently Asked Questions

What is expected of study participants?

- Below are some ways you or the child you care for can be a responsible study participant.
- Provide the study team with complete and accurate information
- Come to the study center for scheduled study visits
- Complete all study tests and procedures
- Update the study team if your contact information changes
- Refrain from participating in another clinical trial or study with an experimental medication
- Tell the study team if you have any concerns or problems making it difficult for you to continue to be in the study
- Avoid nursing or trying to become pregnant since the effect on an infant is unknown. If you become pregnant during the study, notify the study doctor so follow-up visits can be provided
- Refrain from publicly sharing your experiences until after the study is finished. Sharing your experience on the study publicly, including on social media, could unintentionally influence others to choose to participate or not and could result in a delay bringing the therapy to market for patients who need it.

What risks are involved with joining the ADVANCE study?

Since the study medicine is being studied in people for the first time, all the risks are unknown. As with any medication, serious, and in rare instances, fatal allergic reactions can occur. This is why it is important to answer questions completely and truthfully and to tell the study team if any health issues arise during the study.

The study team will monitor study participants closely during infusions to see if there is an allergic reaction to the treatment. If there is an allergic reaction, the study team will give medications to treat and prevent it before the next infusion.

Notify the study doctor immediately if there are any allergic reactions (e.g. rash, itching, feeling unwell). Untreated allergies can lead to a medical emergency.

When will the dosage of study medicine (or placebo) be increased?

If the first two infusions are well-tolerated, the study team will increase the dosage for the study medicine or placebo for the remaining infusions, but the volume and length of the infusion time will not change.

Can study participants decide to leave the study?

Study participants can choose to leave the study at any time. While on this study, other treatments for the symptoms of Farber disease that have been prescribed by a doctor (e.g. paracetamol or tocilizumab) may be continued. However, other investigational treatments may not be taken while participating in the ADVANCE study.

What if something new is learned about Farber disease?

Any new, important information that is discovered during the study that may influence anyone's willingness to stay in the study will be shared by the study doctor.

What benefits are there to joining the study?

Anyone who joins the ADVANCE study may or may not personally benefit from being in this study for treatment of the symptoms of Farber disease. This study is for research purposes only. Information learned from the study may help you or the child you care for and other people in the future. It may also help determine if RVT-801 is useful for treating patients with Farber disease overall.

What do study participants receive for being in the study?

A concierge travel company paid for by Aceragen, the study sponsor, will provide personalized travel services at no cost to all study participants.

Medical information and blood samples collected during this study may be used for the development of new products, processes, or services for commercial sale. The sponsor has no plans to offer financial compensation or share any profits from the sale of any products, processes, or services developed from information and blood samples collected from study participants. However, by signing the informed consent, you or your child will not lose any rights to which you are entitled to by law.

Visit **www.AdvanceFarberStudy.com** for links to resources that may help you better understand clinical research, your rights, and questions to ask your doctor.

Frequently Asked Questions

How is patient privacy protected?

Personal and medical information will be kept confidential, secure, and protected. If the results of this study are published, study participants will not be identified.

Photographs of bumps (nodules) may be used in future presentations or publications about this research study. However, names will not be used with the photographs.

Other information collected, including blood samples, will be kept by the study sponsor for at least two years after any new drug is approved as a therapy for Farber disease.

If you have more questions about how study participants' information may be used, please ask the ADVANCE study team.

What happens if a study participant is hurt during the study?

If you or the child you care for are injured during this study, there may be compensation for medical expenses to treat the injury. The study doctor will discuss the options with you.

How much will it cost to be in the study?

There is no charge to participate in this study. The study-related procedures and study visits will be provided at no charge. The research staff involved in the study will be paid by Aceragen, the study sponsor.

Travel, hotel accommodations, and meals will be paid for by the sponsor. For travel arrangements made through Clincierge®. They will help arrange:

- Hotel accommodations during clinical site visits, if needed
- Travel-related costs (e.g. air, train, car transportation, or bus reservations) for study participant and caregiver, if needed
- Reimbursement for expenses: meals, taxis, parking, mileage, and other approved travel related expenses

Clincierge® will make and pay for the arrangements directly and provide confirmation.

Who do study participants contact with a complaint or problem about the study?

During the study, if you or the child you care for experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor or ask the study team for the contact information for the Institutional Review Board (IRB) or Ethics Committee (EC) who has reviewed this study. An IRB or EC is an independent committee established to help protect the rights of people who participate in clinical research studies[14].

The IRB or EC can also answer any questions about your rights as a clinical research participant or your child's rights.

Can study participants leave the study or be asked to leave the study?

Study participants may choose to not participate or withdraw from the study for any reason without any impact to their standard medical treatment or at any financial cost. The study doctor will ask for a final visit if a study participant leaves the study for any reason.

The study doctor or the sponsor can ask a study participant to leave the study at any time without consent for the following reasons:

- If it appears to be medically harmful
- If the study participant does not follow directions for participating in the study
- If the study participant does not meet the study requirements
- If the study is canceled
- Administrative reasons

References

[1] "What Is a Placebo?" *CISCRP*, www.ciscrp.org/wp-content/uploads/2017/12/What-is-a-Placebo.pdf.

[2] Office of the Commissioner. "Clinical Trials: What Patients Need to Know." *US Food and Drug Administration Home Page*, Office of the Commissioner, www.fda.gov/ForPatients/ClinicalTrials/default.htm.

[3] Office of the Commissioner. "Informed Consent for Clinical Trials." *US Food and Drug Administration Home Page*, Office of the Commissioner, www.fda.gov/ForPatients/ClinicalTrials/InformedConsent/ucm20041763.htm.

[4] "Farber Lipogranulomatosis; FRBRL." *OMIM* (Online Mendelian Inheritance in Man), www.omim.org/entry/228000.

[5] "Farber's Disease." *NORD (National Organization for Rare Disorders)*, rarediseases.org/rare-diseases/farbersdisease/.

[6] "Farber Lipogranulomatosis; FRBRL." *OMIM*, www.omim.org/entry/228000.

[7] "Farber's Disease." *NORD (National Organization for Rare Disorders)*, rarediseases.org/rare-diseases/farbersdisease/.

[8] Ibid.

[9] "ASAH1 Gene - Genetics Home Reference." *U.S. National Library of Medicine*, National Institutes of Health, ghr.nlm.nih.gov/gene/ASAH1.

[10] "All about Lysosomal Storage Disorders." *NTSAD (National Tay-Sachs & Allied Diseases Association)*, www.ntsad.org/index.php/research-for-families/an-introduction-to-research/lysosomal-storagedisorders#faq_22.

[11] "Farber's Disease." *Genetic and Rare Diseases Information Center*, U.S. Department of Health and Human Services, rarediseases.info.nih.gov/diseases/6426/farbers-disease.

[12] "Farber Lipogranulomatosis; FRBRL." *OMIM*, www.omim.org/entry/228000.

[13] "Farber's Disease Information Page." *National Institute of Neurological Disorders and Stroke*, U.S. Department of Health and Human Services, www.ninds.nih.gov/Disorders/All-Disorders/Farbers-Disease-Information-Page.

[14] Office of the Commissioner. "Clinical Trials: What Patients Need to Know - What Patients Need to Know About Institutional Review Boards." *US Food and Drug Administration Home Page*, Office of the Commissioner, www.fda.gov/ForPatients/ClinicalTrials/ucm417961.htm.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