VTAL

Clinical Study

A CLINICAL STUDY TO EVALUATE AN INVESTIGATIONAL, ONE-TIME GENE THERAPY FOR HUNTINGTON'S DISEASE

This clinical study is sponsored by Voyager Therapeutics

BUSINESS CARD
FPO

VYTAL

VYTAL is a clinical study for adults with Stage 1 Huntington's disease. If you were recently diagnosed with Huntington's disease, this clinical study may be an option for you. You should discuss your interest in participating with your doctor. The VYTAL clinical study is evaluating an investigational, one-time gene therapy approach. The study will help inform researchers if the approach is safe and if it has the potential to slow the progression of Huntington's disease.

The doctor at the clinical study site will determine whether you are eligible to participate in the clinical study. You may be eligible to participate if you:

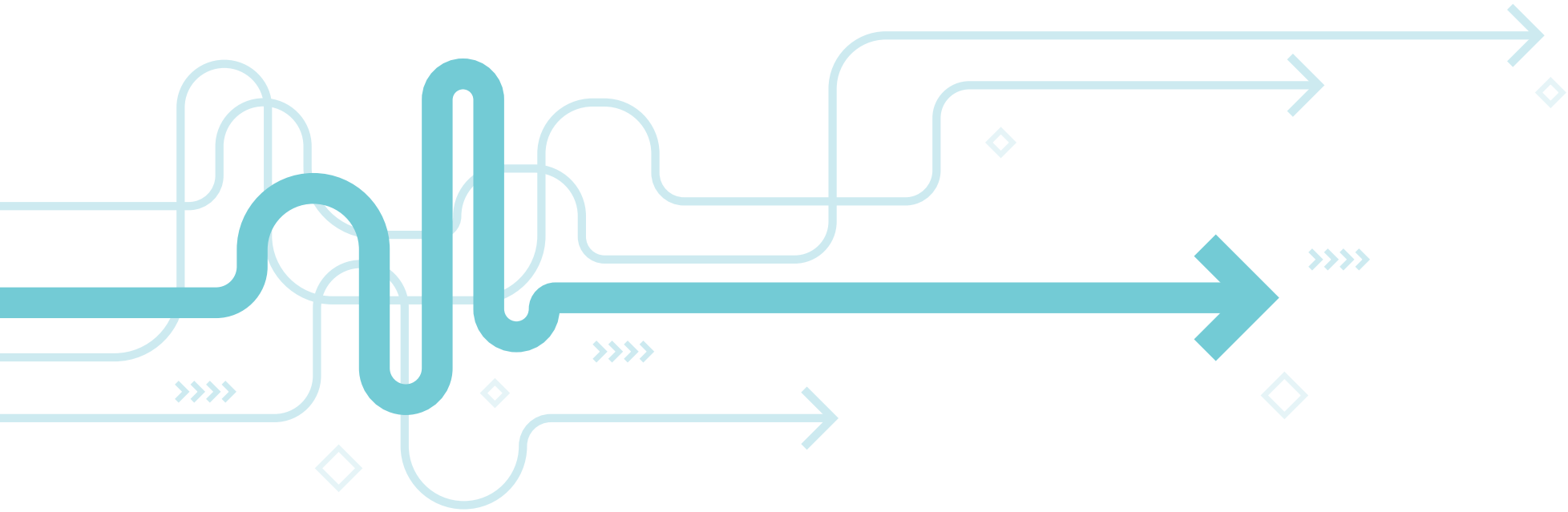
- Are at least 18 years of age
- Have been diagnosed with Stage 1 Huntington's disease
- Have 40 or more cytosine-adenine-guanine trinucleotide (CAGn) repeats
- Do not have severe kidney disease or kidney failure
- Agree to comply with all study requirements, including neurosurgery, MRI, and lumbar puncture
- Are not pregnant or breastfeeding, and are willing to use highly effective contraception for 12 months after surgery
- Agree to complete all required study visits
- Meet other study eligibility requirements

The Role of Huntingtin Protein in Huntington's Disease[1,3]

Huntington's disease is caused by mutations in the huntingtin gene. The huntingtin gene provides instructions for making a protein called huntingtin. Huntingtin protein is believed to play an important role in nerve cells within the brain. The mutation that causes Huntington's disease involves a segment of the huntingtin gene called a CAG trinucleotide repeat. The repeat is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated up to 35 times within the gene. In people with Huntington's disease, the CAG segment is repeated more than 35 times.

An increase to the number of CAG repeats leads to the production of mutant huntingtin protein. Mutant huntingtin protein is abnormally long. It interacts abnormally with other proteins and disrupts the functioning of nerve cells. This leads to widespread nerve cell death, which is responsible for the symptoms and progression of Huntington's disease.

This is why researchers have focused on developing an investigational gene therapy that reduces the amount of huntingtin protein in the brain. This investigational gene therapy is intended to slow the progressive physical, behavioral, and mental decline that occurs in Huntington's disease.



Investigational Gene Therapy for Huntington's Disease

The main purpose of this clinical study is to look at the safety of an investigational gene therapy for Huntington's disease. This study will also look at the effects of the investigational gene therapy on clinical signs and symptoms of Huntington's disease. A surgical procedure will be used to deliver the investigational gene therapy into specific areas of the brain. The investigational gene therapy is intended to reduce levels of huntingtin protein, which may slow the progression of Huntington's disease.[a]

This one-time investigational gene therapy is designed to deliver a gene that produces a small molecule known as a "microRNA" to the brain.

MicroRNAs control the production of specific proteins. The microRNA in this investigational gene therapy is designed to reduce production of huntingtin protein. It is delivered inside an adeno-associated viral vector (AAV). To understand how this works, think of the gene as a letter. The letter contains important instructions on how to prevent huntingtin protein from being produced. The AAV is the envelope that carries the letter.

[a]This gene therapy is investigational and has not been approved by the FDA for use outside of this clinical study.

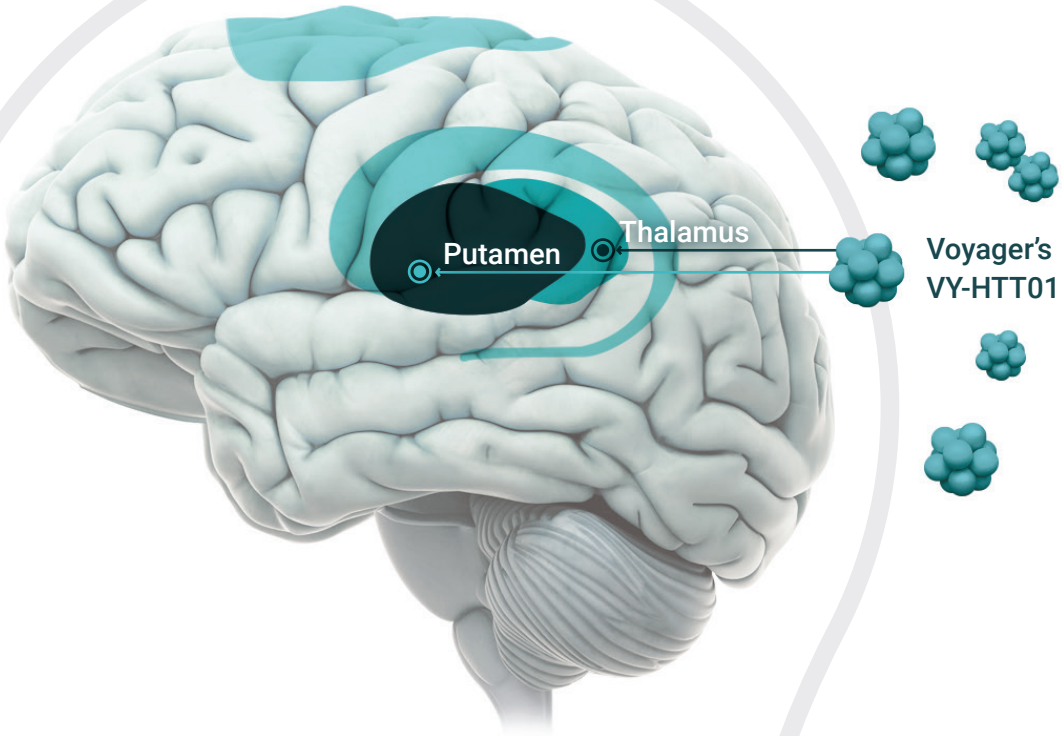
VY-HTT01, Voyager's Investigational Gene Therapy

AAV acts like an envelope. It carries the gene that prevents huntingtin protein production (the letter).

The gene contained in the AAV "envelope" is delivered to specific areas of the brain. These areas are involved in the development and progression of Huntington's disease[1,2] and may allow the investigational gene therapy to travel to other parts of the brain.

Upon delivery, nerve cells in your brain may "open the letter." The cells use the instructions in the letter to produce the microRNA. The microRNA is intended to prevent huntingtin protein production to slow the progression of Huntington's disease.

In Huntington's disease, mutant huntingtin protein is responsible for widespread nerve cell death in the brain and clinical progression of the disease.[1]



Voyager's VY-HTT01

Voyager Therapeutics' investigational gene therapy is designed to introduce a gene to several areas of the brain that is intended to prevent production of huntingtin protein. These brain areas are involved in the development and progression of Huntington's disease.

A Surgical Procedure to Administer the Investigational Gene Therapy

You will undergo a surgical procedure.

The surgical visit will include:

- A full day visit, which includes the surgery
- You being asleep for the entire procedure
- An MRI scan to monitor the procedure
- Administration of the investigational gene therapy via infusion into two specific areas of the brain
- Approximately one to three days in the hospital, including the day you have surgery
- Other requirements as necessary

Before the procedure, you will be randomly assigned to one of two groups: the treatment group or the delayed treatment (control) group. You will have a 75% chance of being assigned to the treatment group.

The study is not blinded. This means that both you and your neurologist will know your group assignment. If you are assigned to delayed treatment, you will still receive the investigational gene therapy after a period of at least 6 months if you continue to meet eligibility requirements.

Treatment Group

If you are assigned to the treatment group, you will receive the investigational gene therapy. The investigational gene therapy will be delivered to areas of your brain involved in the development and progression of Huntington's disease.

Delayed Treatment (Control) Group

If you are assigned to the delayed treatment (control) group, you will undergo many of the same assessments as participants in the treatment group, but will not initially undergo surgery to receive the investigational gene therapy. After an observation period of at least 6 months, you will then undergo surgery to receive the investigational gene therapy if you remain eligible.

Why is a control group needed?

A control group plays an important role in clinical studies. Researchers will compare the results of the delayed treatment (control) group to the results of the investigational gene therapy treatment group. This will help them to understand if any health-related changes occurred because of the therapy or by chance.

All eligible participants will receive the investigational gene therapy. This includes participants assigned to the delayed treatment (control) group, but only if they continue to meet eligibility requirements.

Study Participation Overview

If you are assigned to the treatment group, you will have about 16 visits over a period of up to 15 months. If you are assigned to the delayed treatment (control) group, you will have about 21 visits over a period of up to 24 months.

During these visits, the study doctor and study staff will conduct a number of tests and assessments. Some of the visits will be at the clinic and some may be hybrid visits. Hybrid visits will occur partially at the clinic and partially as a home visit. The location of visits (clinic or home) will be at the discretion of you and your doctor.

The purpose of these tests and assessments is to:

- Determine whether you are eligible to participate
- Monitor your health and well-being in connection with the study
- Assess the safety of the investigational gene therapy
- Gather data that may help researchers better understand the gene therapy

Assessments will be performed at every visit to monitor your safety and Huntington's disease symptoms

Screening, Baseline, and Delayed Treatment Period[a]

	Screening Visit[b,c] (6.5 h)	Baseline Visit[c] (5 h)	Delayed Treatment Period These additional visits apply to patients in the delayed treatment group only Visit 1[c] (2.5 h)	Visit 2[c] (4 h)	Visit 3[c] (6 h)	Visit 4[c] (1.5 h)	Visit 5[c] (6 h)	RSS Visit[d] (6 h)
Date & Time								
Notes								
Brain MRI scan								
Blood draw								
Urine sample collection								
Resting 12-lead ECG								
Lumbar puncture								
Questionnaires and functional tests/exams								

ECG, electrocardiogram; h, hours; MRI, magnetic resonance imaging; RSS, reconfirmation of surgical suitability.

[a]The duration of each visit will depend on the number and type of assessments performed.
[b]Screening visit assessments may occur over multiple days.
[c]Screening, baseline, and delayed treatment follow-up visits may occur at the clinical site or as hybrid visits. Hybrid visits are partially in clinic and partially at your home by video call and with a visiting nurse.
[d]This visit will only occur if delayed treatment visit 5 occurs more than 60 days before surgery.

Assessments will be performed at every visit to monitor your safety and Huntington's disease symptoms

Surgery and Follow-up[a,b]						Follow-up Visits[c]								
	Pre-Op[d] (2 h)	Surgery[e] (11 h)	Peri-Op 1 (20 mins)	Peri-Op 2 (20 mins)	Post-Op[f] (1 h)	Visit 1 (2.5 h)	Visit 2 (4 h)	Visit 3 (6 h)	Visit 4 (1.5 h)	Visit 5 (6 h)	Visit 6 (1.5 h)	Visit 7 (4 h)	Visit 8 (1.5 h)	Visit 9 (6 h)
Date & Time														
Notes														
Brain MRI scan														
Blood draw														
Urine sample collection														
Chest x-ray														
Lumbar puncture														
Questionnaires and functional tests/exams														

h, hours; mins, minutes; MRI magnetic resonance imaging; peri-op, peri-operative; post-op, post-operative; pre-op, pre-operative; RSS, reconfirmation of surgical suitability.

[a]If you are assigned to delayed treatment, you will undergo surgery and complete the follow-up visits only if you remain eligible after completing visit 5 or the RSS visit.

[b]The duration of each visit will depend on the number and type of assessments performed.

[c]Follow-up visits may be completed in clinic or as hybrid visits.

[d]A presurgical consultation with the neurosurgeon and anesthesiologist may occur in person or by video call. The length of the consultation may be more than 2 hours and may vary based on your surgical site's local guidelines.

[e]Surgery will be performed only at a designated surgical site. The timing given (11 h) pertains to surgery and the assessments listed. The full stay for the surgical procedure will span 1-3 days.

[f]Post-operative care will be completed at the clinic.

Brain MRI scan: You will have a magnetic resonance imaging (MRI) scan of your brain. For the MRI scans that do not occur on the day of surgery, you will lie down on a narrow bed that will then be moved into a tunnel that is open at each end. You will lie there quietly for about 1 hour, during which time there will be noises generated by the MRI machine. You may feel warm during this procedure. Before certain MRI scans, you will receive a contrast product. Clinic staff will inject the contrast product by inserting a needle into a vein in your arm.

Blood draw (venipuncture): You will be asked to give a blood sample for laboratory tests. About one to four tablespoons of blood will be drawn by inserting a needle into a vein in your arm for these tests. Arrangements can be made for a study nurse to come to your home to perform the blood draw on days that you do not visit the clinic.

Urine sample collection: You will be asked to provide a urine sample for laboratory tests. Arrangements can be made for a study nurse to come to your home to collect the sample on the days that you do not visit the clinic.

12-lead ECG: An electrocardiogram, or ECG, is a test that records the electrical activity of your heart. Clinic staff will place sticky leads onto 12 sites on the skin of your arms, legs, and chest. Staff will then briefly record your heart rate and your heart's electrical activity. The full procedure will take about 10 minutes.

Chest x-ray: Clinic staff will perform a chest x-ray to measure the size, shape, and location of your heart, lungs, and blood vessels. You will be asked to stand very still next to the x-ray film while holding your breath. The x-ray machine will be turned on for less than one second to generate an image of your chest. X-rays may be taken from more than one view of your chest, such as the front and side. The amount of radiation you will receive is low and not considered dangerous.

Lumbar puncture: The purpose of this procedure is to collect a sample of the fluid that surrounds your brain and spinal cord. The full procedure will take about 45 minutes. You will be asked to lie on your side with your knees drawn to your chest, or to sit upright and lean forward. A study doctor will apply a numbing agent to your lower back and will insert a thin needle between two of your lower (lumbar) vertebrae into your spinal cord. You may feel some pressure in your lower back when the needle is inserted. After collecting a small sample of the fluid in your spinal cord, the study doctor will remove the needle and apply a bandage to your back.

Questionnaires and functional tests/exams: You will be asked to complete some questionnaires and take some tests related to your day-to-day functioning. These assessments will provide information about your Huntington's disease symptoms and quality of life. You may be able to complete some assessments at home. You will also undergo physical and neurological exams with a study doctor. These may occur over video call.

Study-Related Care, Reimbursement, and Travel Assistance

Study-related care, including the surgery, clinic visits and assessments, and study treatment will be provided at no cost. Reimbursement for study-related activities (meals, transportation, parking, etc.) may be provided.

In addition, full-service travel assistance including transportation to study visits for you and a care partner may also be available. To learn more about these services, please speak with a member of the study staff.

It's Time to Talk About Your Options

Participating in the VYTAL Clinical Study is completely voluntary. Before you decide whether or not you want to participate, a study doctor will speak with you. The study doctor will review the potential risks and benefits in detail and will answer any questions that you may have. Talk with the study doctor if you have any questions regarding this study. You may also want to talk with your own doctor about your participation in the study. You should discuss any questions you have about your medical condition, care, and treatment with your doctor.

Interested in learning more about the VYTAL study?
Speak with a member of the study team today.

References

1. McColgan P & Tabrizi SJ. *Eur J Neurol*. 2018;25(1):24-34.
2. Halliday GM et al. *Exp Neurol*. 1998;154(2): 663-672.
3. Rubinsztein DC et al. *Am J Hum Genet*. 1996;59(1):16-22.