Frequently Asked Questions
Clinical Trial of AGT-182 in Adult Patients with Hunter Syndrome

(AGT-182-101)

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What is a clinical trial?

A clinical trial is a research study that explores the safety and/or effectiveness of a potential new treatment in humans.

Why should I participate in a clinical trial?

People choose whether or not to participate in clinical trials for various reasons. Participation in clinical trials can provide early access to treatments being studied for safety and effectiveness, expert medical care, and the opportunity to contribute to medical research and potentially help future generations of people with the disease being studied. Speak with your physician for guidance on whether to enroll in a trial.

Who oversees clinical trials?

To ensure the safety and welfare of patients, clinical trials are overseen by national health agencies. In addition, each clinical trial site appoints an Institutional Review Board (IRB) to review, monitor and approve medical research.

What is Hunter syndrome?

Hunter syndrome is a rare, hereditary metabolic disorder that primarily affects males. In people with Hunter syndrome, an enzyme called iduronate 2-sulfatase (IDS) is missing or does not work properly. This leads to an abnormal buildup of complex sugars in tissues throughout the body, including the skeleton, joints, brain, spinal cord, heart, spleen and liver.

Hunter syndrome is often severe and always progressive. It affects the brain and spinal cord, resulting in debilitating signs and symptoms. When severe, these symptoms can include developmental delay, behavioral challenges and progressive mental decline. Hunter syndrome also affects the body resulting in loss of physical function, impaired language development (due to hearing loss and an enlarged tongue), possible corneal and retinal damage, carpal tunnel syndrome and restricted joint movement. Hunter syndrome is also known as mucopolysaccharidosis type II, or MPS II.

What is AGT-182?

AGT-182 is an investigational enzyme replacement therapy (ERT) designed to treat the symptoms and complications of Hunter syndrome both in the body (somatic) and central nervous system (CNS), consisting of the brain and spinal cord.

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Currently approved treatments for Hunter syndrome are unable to cross the blood-brain barrier (BBB). The BBB is a filter that protects the brain from toxins but allows vital nutrients like insulin to cross from the blood into the brain. As a result, available therapies do not address many of the severe and progressive neurological complications of Hunter syndrome.

AGT-182 is designed to cross the BBB in the same way insulin does. AGT-182 is not approved by the U.S. Food and Drug Administration.

How is AGT-182 different from existing therapies such as Elaprase®?*

Approved treatments for Hunter syndrome are unable to penetrate the blood-brain barrier (BBB), and therefore do not address many of the severe and progressive neurological complications of the disease. AGT-182 is designed to cross the BBB in the same way insulin does.

Do AGT-182 and Elaprase contain the same active ingredient?

AGT-182 and Elaprase both contain a replacement IDS enzyme. However, AGT-182 is designed to treat both the body (somatic) and central nervous system (CNS) consisting of the brain and spinal cord). AGT-182 transports IDS across the blood-brain barrier (BBB) by targeting the same receptor that delivers insulin to the brain. The ability to cross the BBB makes AGT-182 unique among treatments for Hunter syndrome.

A study published in *BioConjugate Chemistry* in 2013 showed extensive distribution of AGT-182 to all regions of the brain of a rhesus monkey within two hours of intravenous (IV) injection. By contrast, Elaprase was only distributed to the peripheral tissues of the brain.[1]

How is AGT-182 different from intrathecal idursulfase?

AGT-182 and intrathecal idursulfase are not approved for the treatment of Hunter syndrome. One important difference between these investigational therapies is the method of administration. Intrathecal idursulfase is injected using a drug delivery device through the spinal canal into the cerebrospinal fluid (the fluid that circulates to the brain), while AGT-182 is administered by intravenous (IV) infusion to treat both the body (somatic) and central nervous system (CNS), consisting of the brain and spinal cord.

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* Elaprase is a registered trademark of Shire Human Genetic Therapies, Inc.

What is the blood-brain barrier (BBB)?

The BBB is a barrier that filters substances crossing from the blood into the brain. It protects the brain from bacteria and other foreign substances, but allows the passage of vital nutrients that are required for the proper health and function of the brain. Insulin is one example of a substance that can get into the brain through the BBB. AGT-182 is an investigational therapy designed to cross the BBB in the same way insulin does.

What is the purpose of the Phase 1 clinical trial of AGT-182?

The purpose of this Phase 1 clinical trial is to test the safety and determine a well-tolerated dose of AGT-182 for the investigational treatment of patients with Hunter syndrome.

What is the name of the trial, and where can I find more information?

The trial is called the Breaking Barriers clinical trial of AGT-182-101. You can find more information on www.clinicaltrials.gov using the identifier number NCT02262338.

What is a Phase 1 clinical trial?

A Phase 1 clinical trial tests a new drug in a small group of patients to evaluate the drug's safety, identify potential side effects, and determine a dose of the medication for further testing.

What is the design of the Phase 1 clinical trial of AGT-182?

Enrolled patients will receive AGT-182 weekly for a total of eight weeks.

Importantly, all patients enrolled in the trial will receive investigational treatment with AGT-182. There is no control group in the study, and no patients will receive a placebo treatment.

How will AGT-182 be dosed in the trial?

Patients in the trial will receive weekly infusions of AGT-182 at assigned doses that range from 1.1 for the first cohort (dose group) of patients enrolled and increase to 3.0 mg/kg. Potentially higher doses will be given, up to 9.0 mg/kg if the 3 mg/kg dose does not appear to have an effect on urine disease markers called glycosaminoglycans (GAGs) after 8 weeks. The drug solutions will be administered intravenously (IV) over a 3-hour period.

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How are patients evaluated to determine eligibility? How do I sign up?

You can learn more about the study and enrollment process by calling the investigators at the study centers listed on www.clinicaltrials.gov using the identifier number NCT02262338, or by referring to the list available on the Breaking Barriers website. The study centers will evaluate your eligibility and review next steps with you.

Who is eligible to participate in this clinical trial?

The trial is open to adult males (age 18 years or older) who have been diagnosed with Hunter syndrome. Patients must fall into one of the following groups:

- Be currently receiving and be willing to discontinue enzyme replacement therapy (ERT) for a 6-week washout period and for the remaining duration of their participation in the trial (washout group).
- Have not received ERT for at least three months (extended washout group) and have elevated mucopolysaccharides, complex sugars that can interfere with functioning of certain cells and organs when elevated, at least 3.5 times greater than age-related normal values at the beginning of the study.
- Have never received ERT (Treatment-Naïve Group) and have elevated mucopolysaccharides at least 3.5 times greater than normal at the beginning of the study.

You can learn more about the study and eligibility criteria by calling the investigators at the study centers listed on www.clinicaltrials.gov using the identifier number NCT02262338, or by referring to the list available on the Breaking Barriers website. The study centers will evaluate your eligibility and review next steps with you.

Why is the trial being conducted in patients without involvement of the central nervous system?

The clinical trial protocol is based on discussions with regulatory agencies and physician experts in lysosomal storage disorders. As is common in Phase 1 clinical studies, the trial is designed to evaluate safety in a broad range of patients, including those without neurological complications.

The trial will help us determine an appropriate dose of AGT-182 for testing in future clinical trials in a cognitively impaired pediatric age group.

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Are there any reasons a patient may not participate in this trial?

There are a few factors that make patients not eligible for the trial. Examples include if the patient has:

- Received an investigational drug within the past 90 days.
- A medical condition or serious illness that, in the opinion of the investigator, may significantly interfere with study compliance.
- Clinically significant spinal cord compression or evidence of cervical instability.

If patients are not eligible for the clinical trial, can they still get access to the medication?

ArmaGen, the sponsor of this study, believes that participating in clinical trials is the best way for patients to access medicines prior to regulatory approval. To ensure there is sufficient safety and efficacy data available, the sponsor does not consider requests for expanded or compassionate use outside the clinical trial setting until the conclusion of the pivotal clinical trial.

What kinds of side effects may be associated with AGT-182?

Patient safety is a priority for the sponsor of the study, the investigators and the patient community. Subjects will be monitored for potential side effects associated with AGT-182 that may include urticaria (hives), rash, malaise (a general feeling of being unwell), shortness of breath, hypoxemia (abnormally low levels of oxygen in the blood), hypotension (abnormally low blood pressure), tachycardia (a rapid heartbeat), nausea, chills, fever or abdominal pain.

What happens if a clinical trial participant experiences side effects?

If a patient experiences a side effect or adverse event during the clinical trial, the appropriate clinical treatment will be prescribed. Patients can choose to stop participating in the clinical trial at any time. If an adverse event is present when the patient withdraws from the study, the patient will be re-evaluated within 2 weeks of withdrawal. If the adverse event has not resolved at that time, additional follow-up will be performed as appropriate.

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Where is the trial being conducted?

The trial will be conducted at specific academic centers specializing in Hunter syndrome located in the USA and Europe.

Is there a cost associated with participating in the trial? Will patients be paid to participate in the trial?

We understand that participating in a clinical trial is a significant commitment of time and, potentially, resources for families. There is no cost to participate in the trial and all tests will be provided to patients at no cost. We are committed to helping families manage the travel, logistics and expenses of participating in the trial. Patients in the clinical trial will not be paid.

Will ArmaGen cover transportation and housing to patients who live far from the site?

Study centers will provide more information on reimbursement of expenses. Reimbursement of travel and housing costs will be evaluated on a case-by-case basis.

Who is sponsoring the clinical trial?

The trial is sponsored by ArmaGen, a privately held biotechnology company focused on developing revolutionary therapies for severe neurological disorders.

Is Shire involved in this clinical trial?

In July 2014, ArmaGen and Shire entered into a worldwide collaboration and licensing agreement to develop AGT-182 for the treatment of Hunter syndrome. ArmaGen is responsible for conducting the Phase 1 study of AGT-182 in collaboration with Shire, who will provide R&D funding for the trial. This partnership is designed to speed the development of AGT-182.

In announcing the partnership, ArmaGen noted, “Shire is the ideal partner for AGT-182, based on the company’s international reach and expertise in serving patients with Hunter syndrome.”

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[1] Boado, RJ, et al. Blood-Brain Barrier Molecular Trojan Horse Enables Imaging of Brain Uptake of Radioiodinated Recombinant Protein in Rhesus Monkey. Bioconjugate Chemistry 2013; 24:1741-1749. DOI: 10.1021/bc400319d.