Clinical Trial Information for Sanfilippo Syndrome Type A

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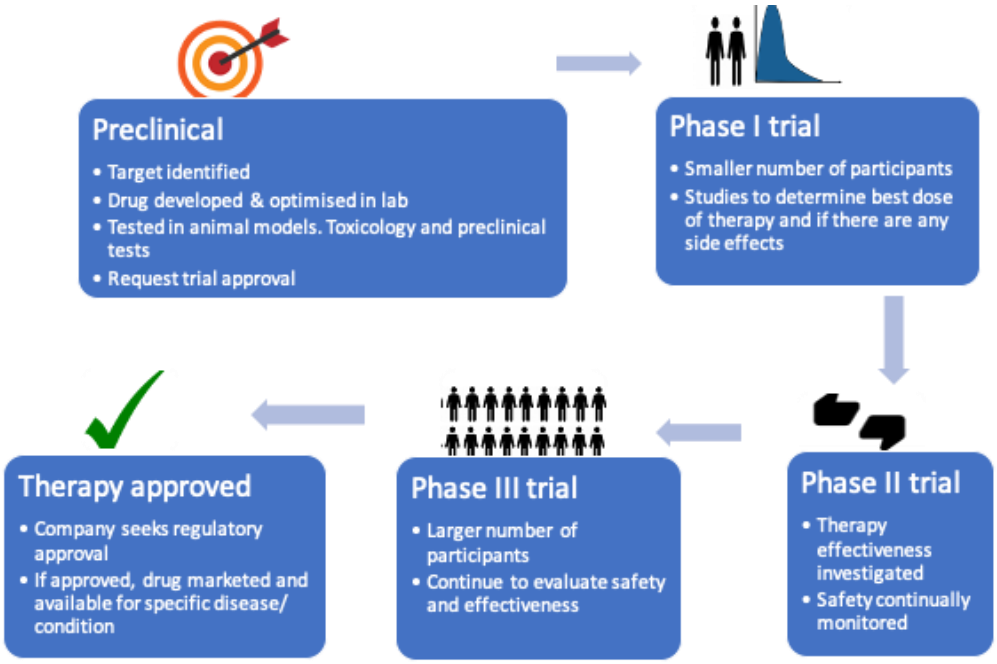
Sanfilippo Children's Foundation

Introduction

The aim of a clinical trial is to determine whether a potential treatment is safe and that it works. Clinical trials involving rare diseases may be run differently to a usual clinical trial, often due to the small number of people with the disease. The process may be shorter than a usual clinical trial, and different phases may be combined. The diagram below outlines some common steps seen in the drug development process:



There are criteria that must be fulfilled in order to be included in a clinical trial. Similarly, there can be criteria that may render someone unable to participate. These strict criteria are chosen by the company carrying out the trial, to protect the safety of the trial participants and to give the trial the best chance of proving that the therapy works.

A well-executed clinical trial that proves a therapy to be safe and effective offers the best chance at getting regulatory approval and allowing more patients to access it.

Participating in a clinical trial is not a guarantee of a treatment, as not all therapies are proven to be safe and effective; however, at this point in time, clinical trials offer the only hope of getting early access to potential Sanfilippo treatments.

This document contains information on clinical trials for Sanfilippo Syndrome Type A – a table with a brief overview, a more detailed description and a handy glossary at the end. If you have any questions about this document or would like more information about Sanfilippo and/or clinical trials, please contact the Foundation.

For more information contact the Research Manager at the Sanfilippo Children's Foundation: research@sanfilippo.org.au

Sanfilippo Syndrome Type A Clinical Trials

Company	Trial	Trial Location (s)	Type of Therapy	Mode of Administration	Important Inclusion/ Exclusion Criteria *(note: other criteria may also apply)*	Current Results/ Progress (that has been made public)	Trial status
Abeona Therapeutics, Inc	Type A trial for younger, higher-functioning patients (Transpher A Study) Phase I/II.	Australia, USA and Spain	Gene Therapy (using AAV9 delivery virus)	Single intravenous injection (into the bloodstream)	**Inclusion**: Age 6 months to approx. 2 years (dependent on cognitive testing - Developmental Quotient (DQ) greater than 60). **Exclusion**: Previous exposure and antibodies to the AAV9 virus (up to 20-30% of children are excluded for this reason). Children with attenuated (less severe) forms of Sanfilippo are unable to take part.	16 Sanfilippo Type A patients (and 9 Type B patients) have been treated so far. The gene therapy appears to be safe. Reduced heparan sulfate in the urine and cerebral spinal fluid (CSF) has been reported, as well as reduced liver and spleen sizes. Full information on cognitive function is not yet available, though there are encouraging signs seen in younger children.	Recruiting
Abeona Therapeutics, Inc	Type A trial for patients with middle and advanced phases of Sanfilippo disease (ABT-003) Phase I/II.	Australia and Spain	Gene Therapy (using AAV9 delivery virus)	Single intravenous injection (into the bloodstream)	**Inclusion**: No age range. Participants must have a Cognitive Developmental Quotient (DQ) less than 60. Must be ambulatory (able to walk) though can have assistance to walk. **Exclusion**: Previous exposure and antibodies to the AAV9 virus. Children with attenuated (less severe) forms of Sanfilippo are unable to take part.	The first participant was enrolled late Oct 2019. No results as yet.	Recruiting
Lysogene	Type A trial, using product named LYS-SAF302.	USA, France, Netherlands and UK.	Gene Therapy (using AAVrh10 delivery virus)	Single intra-cerebral injection (directly into the brain)	**Inclusion**: 6 months and older. Developmental Quotient (DQ) greater than 60. **Exclusion**: Participation in another gene or cell therapy trial. Past use of enzyme replacement therapy for a period greater than	Phase I/II trial (now concluded) included 4 children and showed the therapy appears safe, and the youngest child showed some signs of cognitive improvement. A phase II/III trial has begun with a modified gene therapy product	Active, no longer recruiting. Paused by FDA in June 2020

	Phase II/III.				3 months. Children with attenuated (less severe) forms of Sanfillipo are unable to take part.	and is expected to recruit 20 participants. At the WORLD meeting (Feb 2020), Lysogene reported the treatment of 15 patients but did not present any results. In June 2020, with 19 patients treated, the FDA put a hold on the study due to MRI anomalies. The estimated study completion is Jan 2022.	
Esteve	Type A trial Phase I/II.	Barcelona	Gene Therapy (using AAV9 delivery virus)	Single intra-cerebro-ventricular (ICV) injection (directly into the CSF).	**Inclusion**: 2 years and older. Onset of symptoms within the first 6 years of life. Participants must undertake cognitive testing and score within a certain range. **Exclusion**: Participation in another gene/cell/enzyme replacement therapy trial (past or present). Previous exposure and antibodies to the AAV9 virus. Wheelchair dependence.	Esteve plans to recruit 6 patients for this initial clinical trial. No results have yet been released.	Recruiting
Orchard Therapeutics	Type A autologous ex-vivo gene therapy Phase I/II.	UK	Stem cell-based Gene Therapy	Patient's stem cells taken from blood/ bone marrow. A virus delivers the healthy gene copy into these cells and they are transplanted back into the patient.	**Inclusion**: Between 3-24 months of age. Normal cognitive function or only mild deterioration. Indications of rapidly progressing disease. **Exclusion**: Participation in another gene/cell/enzyme replacement therapy trial (past or present).	Previous to the commencement of the Phase I/II trial, a two-year-old boy with Sanfilippo Type A received this experimental therapy. There was an increase in enzyme activity and reduced GAGs in the urine, CSF and plasma. No cognitive data as yet. For the Phase I/II Orchard trial, one child has been recruited so far.	Recruiting

Swedish Orphan Biovitrum (SOBI)	Type A trial using SOBI003 Phase I/II.	USA, Germany and Turkey	Enzyme Replacement Therapy	Weekly intravenous injection of the missing enzyme.	**Inclusion**: Between 1-6 years age at the time of first infusion. Developmental age of 1 or more at screening. **Exclusion**: Participation in another gene/ stem cell/ enzyme replacement therapy trial (past or present).	There were 9 children who received treatment in the trial, and they are continuing treatment in an extension study. No results reported yet. SOBI is looking for another company to take over the program.	Active, not recruiting
Lundquist Institute for Biomedical Innovation	Anakinra drug (all types of Sanfilippo) Phase II/III.	USA	Anti-inflammatory drug (already approved for rheumatoid arthritis)	Subcutaneous injection of drug (under the skin) once a day	**Inclusion**: Ages 4+. All Sanfilippo Types. Attenuated patients accepted. **Exclusion**: Current participation in another clinical trial. Previous or current treatment with specific anti-inflammatory drugs. Severe liver or kidney disease/ impairment.	No results released so far.	Active, not recruiting

Please note: If your child does not meet the strict criteria for a Clinical Trial, it does not mean they will be unable to receive that treatment in the future (if the clinical trial is successful and the therapy is approved).

Current Clinical Trials and Clinical Trial Plans for Sanfilippo Type A

Updated July 2020

Gene therapy clinical trials

Abeona Therapeutics gene therapy for Sanfilippo types A and B

Abeona Therapeutics is conducting clinical trials of gene therapy for Sanfilippo types A and B and currently has sites in the USA, Spain and Australia (type A only). The first trial for Sanfilippo type A started in the USA in May 2016 and the first Australian patients were treated at Adelaide's Women's and Children's Hospital in 2017.

The program is the result of a unique collaboration between patient groups and researchers at Nationwide Children's Hospital in Ohio together with Abeona. The phase I/II trial was funded by international patient groups, including the Sanfilippo Children's Foundation.

Participants in the clinical trials are administered the gene therapy product intravenously (into the bloodstream). The gene therapy consists of a virus (AAV9) which has the ability to cross the blood-brain-barrier to deliver a healthy copy of the gene that is faulty in Sanfilippo Types A or B.

Encouraging results have been reported - the gene therapy appears to be safe and reductions in heparan sulfate, the toxic substance that builds up in children with Sanfilippo, have been seen in both the urine and the cerebral spinal fluid (CSF). The liver and spleen, which are enlarged in children with Sanfilippo, has reduced.

Sixteen patients with Sanfilippo type A and nine with type B have been treated so far. Full information on the effect on cognitive function is not yet available but the trial continues to show encouraging signs of stabilisation in cognitive tests in younger children.

The inclusion criteria for the main trials have been narrowed to children between the ages of 6 months and approximately 2 years (depending on cognitive testing). To be eligible children also must have not previously been exposed to the AAV9 virus that is used to deliver the gene therapy. AAV9 is a harmless virus that exists in the environment. A blood test will be done to see if the child has antibodies to the virus – up to 20-30% of children are excluded for this reason.

There is also a separate arm of the type A trial now recruiting some older, more advanced patients (ABT-003).

Please see eligibility criteria on clinicaltrials.gov:

- Sanfilippo type A trial for younger, higher-functioning patients (Transpher A Study)
- Sanfilippo type A trial for patients with middle and advanced phases of Sanfilippo disease (ABT-003)

- Sanfilippo type B trial (Transpher B Study)

Lysogene gene therapy trial for Sanfilippo type A

Lysogene was founded by Karen Aiach, mother of a Sanfilippo Type A child in Paris, France. In 2013, Lysogene successfully completed a Phase I/II clinical trial for its gene therapy product SAF-301: four children affected by Sanfilippo Type A were administered a gene therapy product directly into the brain. This involved surgery to inject virus (AAVrh10) carrying a healthy copy of the SGSH gene directly into the brain (intra-cerebral injection).

The Phase I/II trial concluded with good safety results and promising indicators of efficacy. Some alterations have been made to the gene therapy product, now named LYS-SAF302, and a Phase II/III trial has begun. It is expected the trial will recruit 20 Sanfilippo Type A patients at sites in the USA, France, UK, Germany and the Netherlands, more details of the trial are available here.

At World meeting February 2020, Lysogene said that they have treated 15 patients, from 13 months to 65 months of age, but did not present any results.

In June 2020, it was announced that the study was put on hold by the FDA due to MRI findings confined to the sites of therapy injection. In a press release, the company said that 19 of the planned 20 participants had been enrolled and treated so far, and they will continue to be closely monitored. Lysogene does not anticipate any impact on the current clinical trial timelines.

Esteve Sanfilippo Type A gene therapy trial

Pharmaceutical company Esteve is currently recruiting for a Phase I/II gene therapy clinical trial in Barcelona for Sanfilippo Type A.

The treatment approach consists of a single injection into the cerebrospinal fluid of a virus (AAV9) carrying a healthy copy of the SGSH cerebral spinal fluid (CSF) (Intracerebroventricular (ICV) injection). They plan to recruit six patients for this initial clinical trial. No results from this trial have been released.

Esteve is also developing a similar gene therapy approach for Sanfilippo type B, but this is not yet in clinical trial.
For more information, visit Esteve's Sanfilippo program and the European Clinical Trials Register.

Orchard Therapeutics' stem cell-based gene therapy program for Sanfilippo Types A and B

Dr Brian Bigger from The University of Manchester has developed an "autologous ex-vivo gene therapy" for Sanfilippo types A and B. It works by taking the patient's own stem cells

(from the blood or bone marrow) and using a virus to deliver a healthy copy of the faulty gene (SGSH for Type A or NAGLU for Type B). These cells are then transplanted back into the body.

Bone marrow transplants have been previously tried as a treatment for Sanfilippo, but they were largely unsuccessful because the cells did not produce enough of the enzyme that is missing. This approach aims to boost the amount of enzyme produced by the transplanted cells and has the advantage that the patient's own cells are used, lowering the risk of transplant rejection.

The University of Manchester has signed a licensing agreement with Orchard Therapeutics to bring its stem cell gene therapy program to human clinical trial. The type A therapy is currently in a clinical trial and type B is in the pipeline.

In May 2019 it was announced that a two-year-old boy with Sanfilippo Type A received this experimental therapy in Manchester in January, under what is called a "Specials" licence. At the WORLD conference (Feb 2020) the results from this boy were presented. GAGs were reduced in urine, blood and CSF. No cognitive data as yet.

Orchard Therapeutics has now launched a full trial at Royal Manchester Children's Hospital. For more information, please read the summary on clinicaltrials.gov.

Enzyme replacement therapy clinical trials

SOBI's SOB1003 for Sanfilippo Type A

SOBI, a biopharmaceutical company based in Stockholm, is conducting a clinical trial of an Enzyme Replacement Therapy product which is called "SOBI003". There are trial sites in the USA, Germany and Turkey. The first patient was dosed in August 2018.

SOBI003 is a version of the enzyme that is missing in Sanfilippo Type A which has been chemically modified so that it lasts for longer inside the body, giving it more of a chance to get inside cells and do its job of breaking down GAGs.

In June 2019 SOBI announced that it is now looking to divest SOBI003, so the future of this program is uncertain. No more recruitment to the trial but treatment of the 9 kids in the trial is continuing. SOBI is looking for someone to take over the program.

For more information visit clinicaltrial.gov

Other targets

Researchers are working to find other drugs that may reduce the progression of Sanfilippo and improve quality of life, these include:

- Substrate reduction therapies to reduce the amount of heparin sulphate that is produced by the body so that there is less to build up
- Chaperones that help the faulty enzymes fold correctly and do their job of breaking down heparin sulphate
- Drugs that increase a process called “autophagy” that clears unnecessary or dysfunctional components from cells, allowing them to function better
- Drugs to target certain parts of the immune system that are thought to contribute to the cognitive decline seen in children with Sanfilippo
- Treatments targeting the symptoms of the disease such as behavioural problems, sleeping issues or lung function, which aim to improve the quality of life of children with Sanfilippo and their families.

There are two trials in this category, either started or being planned:

- Anakinra, a drug that suppresses inflammation, is in clinical trial at the Lundquist Institute (formerly LA Biomed) in the USA. Cure Sanfilippo Foundation is a collaborator on this trial. This drug is approved for the treatment of rheumatoid arthritis (RA). A Phase II/III trial is currently underway. Very wide inclusion criteria for this trial – all ages, types and attenuated patients. More information about this trial: https://clinicaltrials.gov/ct2/show/NCT04018755
- A clinical trial of Trehalose, a small sugar, is being planned by Seelos Therapeutics and Team Sanfilippo in the USA and Europe. Trehalose is to be given intravenously (through the vein). It is able to enter the central nervous system (the brain and spinal cord), stabilise proteins, and promote autophagy, a process to dispose of aggregated proteins and other cellular waste. Clinical trial design currently being negotiated with the FDA and EU.

Other clinical study opportunities:

Researchers in Adelaide are creating neuronal cell models from cells donated by Australian children with Sanfilippo. These cell models will be used to screen large libraries of existing drugs with many different modes of action, to see if any can be repurposed to alleviate symptoms. Read about the ‘Brain in a Dish’ project.

Adelaide researchers are also looking for a way to accurately monitor the progression of Sanfilippo, which will be very important for future clinical trials. The study will evaluate whether high resolution photographs of the eye provide a non-invasive way to determine how the disease is affecting the brain. More information about this study ‘Is the eye a window to the brain for Sanfilippo syndrome’.

Glossary

Adeno-associated virus (AAV)

An adeno-associated virus is a specific virus that is able to infect humans, but not currently known to cause disease. Because of these features, researchers want to use this virus as a delivery vehicle, in order to deliver therapies into cells. There are many different variants of AAV that occur (both naturally and engineered) such as AAV9 and AAVrh10, and some can cross the blood-brain barrier.

Attenuated form

An attenuated form of Sanfilippo is one that is less severe and/or slower to progress than a severe Sanfilippo form. Whether an individual has a severe or attenuated form of Sanfilippo largely depends on the type of genetic change that the individual has. The S298P genetic change is commonly noted for exclusion, as individuals with this tend to have an attenuated form of Sanfilippo.

Blood-brain barrier

The blood-brain barrier (BBB) is a very thin layer of cells that separates the blood from the central nervous system (CNS). It is highly selective, meaning that only specific things are able to exit the bloodstream and enter the CNS. This helps to protect the brain from harmful bacteria and viruses, but it can hinder the effectiveness of therapies that must cross the BBB to work in the brain.

CNS (Central nervous system)

The CNS is comprised of the brain and the spinal cord.

Clinical Trial

Clinical trials are research studies that test a specific therapy in humans, with the aim of confirming whether a therapy is safe and effective to be used in a specific population.

CSF (Cerebrospinal fluid)

Cerebrospinal fluid (CSF) is the fluid that bathes the brain and the spinal cord. It helps to protect the brain and spinal cord in the case of trauma and helps to supply nutrients and remove waste products.

Developmental quotient (DQ)

Developmental quotient (DQ) is a number used to measure a child's development and determine whether there is a developmental delay. DQ is calculated based on the result of neuropsychological test(s) compared to the child's chronological age.

Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy involves the delivery of functional enzyme into the body. In MPS IIIA, the enzyme that needs to be replaced is called sulfamidase.

Gene Therapy

Gene Therapy involves the delivery of a healthy copy of a gene into the body. The four subtypes of Sanfilippo correspond to four different genes. For MPS IIIA, the gene involved is called *SGSH*.

Heparan sulfate

Heparan sulfate is a complex, long, linear sugar molecule found in the body. It is an important molecule that is made by the body, but also must be broken down after use. In Sanfilippo Syndrome, one of the four enzymes involved in degrading heparan sulfate is faulty.

Intracerebral injection

An intracerebral injection is an injection directly into the brain. This represents a straightforward way of delivering agents to the brain that may be unable to cross the blood-brain barrier, though the procedure is more invasive.

Intracerebroventricular injection

An intracerebral injection is an injection directly into one or more areas of the brain that produces CSF. This also represents a straightforward way of delivering agents to the brain that may be unable to cross the blood-brain barrier, though the procedure is more invasive.

Intravenous injection

An intravenous injection is an injection directly into the vein. Common sites include the elbow, wrist, or back of the hand.

Phases of clinical trial

Clinical trial Phases are different stages or steps with different goals and experimental set ups. Traditionally, there are four stages: I, II, III and IV. The increasing numbers represent a more advanced stage of the clinical trial.

Stem cells and stem cell therapy

Most cells in the body are specialised, such as muscle cells or red blood cells. These specialised cells perform very specific roles and often have a set lifespan before they must be replaced. In contrast, stem cells can make more stem cells ('self-renewal'), or they can make cells that will turn into specialised cells ('differentiation').

Stem cell therapy involves the use of stem cells to treat disease. A well-known example is bone marrow transplant for leukaemia. For genetic diseases like Sanfilippo, one way of using stem cells would be to collect stem cells from a patient (e.g. from the bone marrow), and a healthy gene copy inserted into these cells in the laboratory. The new stem cells can then be returned back to the patient. Orchard Therapeutics has stem cell therapy for MPS IIIA and IIIB in its research pipeline.

It is important to ensure that any therapies, including stem cell therapies, have the appropriate regulatory approval. In some parts of the world, there are unregulated stem cell therapy clinics, which market therapies that are unproven and potentially dangerous (see here for more information from the FDA).

Subcutaneous injection

A subcutaneous injection is an injection directly under the skin, between the skin and muscle.

Substrate reduction therapy (SRT)

Substrate reduction therapy aims to reduce the amount of substrate involved in a disease state, in order to improve symptoms. In the case of Sanfilippo, SRT involves therapies that aim to decrease the amount of heparan sulfate, which normally builds up to toxic levels inside the body.