Clinical Trial Information for Sanfilippo Syndrome Type B

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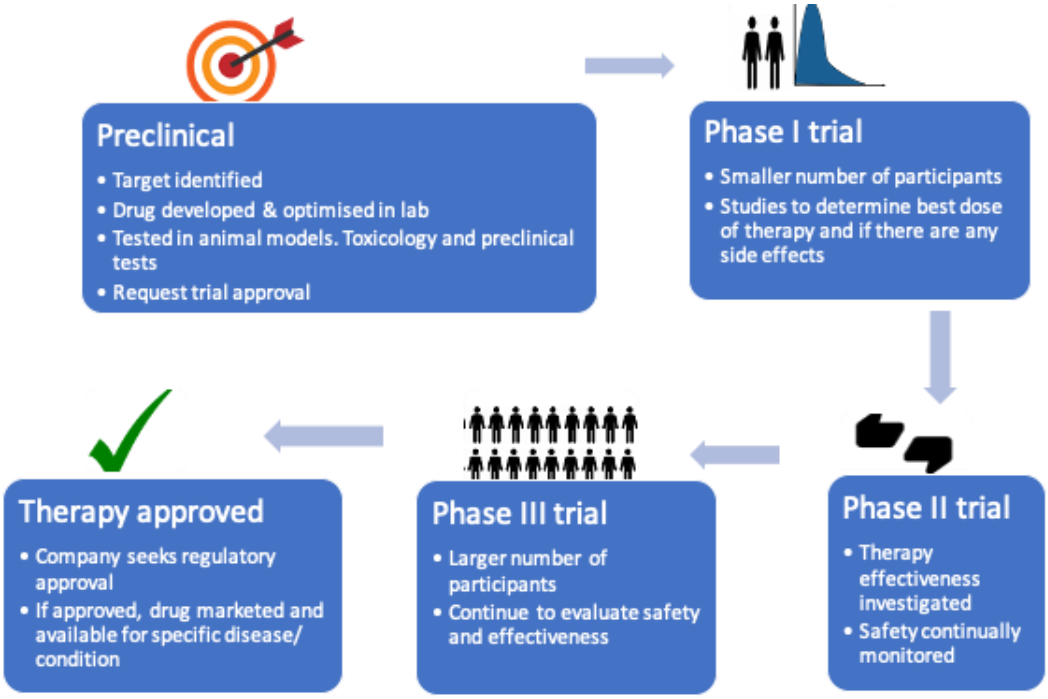
Sanfilippo Children's Foundation

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 B – 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 B Clinical Trials

Company	Trial	Trial Location(s)	Type of Therapy	Mode of Administration	Important Inclusion/ Exclusion Criteria (note: others may also apply)	Current Results/ Progress (that has been made public)	Trial status
Abeona Therapeutics, Inc	Type B trial (Transpher B Study) Phase I/II. Note: Type A also studied in Australia, USA and Spain	USA, France, Germany and Spain	Gene Therapy (using AAV9 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.	9 Sanfilippo Type B patients (and 16 Type A patients) have been treated so far. The gene therapy appears to be safe. Reduced heparan sulfate in the urine and cerebral spinal fluid (CSF) of Sanfilippo children 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
Allievex (formerly Biomarin)	Type B trial with Tralesinidase Alfa Phase I/II.	Columbia, Germany, Spain, Taiwan, Turkey, USA and UK	Enzyme Replacement Therapy	Weekly administration direct into the cerebrospinal fluid (CSF) of the brain via a port implanted under the scalp	**Inclusion**: Ages 1-10. Participants must be able to undertake study procedures and evaluations (e.g. neurosurgery, MRIs, neurodevelopmental testing).	The trial is active but not currently recruiting. At the 2018 WORLD Symposium, it was reported that 6 children had been given treated at different dose levels. Heparan sulfate decreased in the CSF to	Active, not recruiting

					Exclusion: Current participation in another MPS IIIB clinical trial. A history of poorly controlled seizures.	normal levels, and livers reduced to normal size in these children. At the highest dose there was some indication of cognitive stabilisation – further evidence is required. Side effects were noted due to the invasiveness of the therapy. The company is preparing to go to the FDA for drug approval.	
Lundquist Institute for Biomedical Innovation	Anakinra drug trial (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 B

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. Current type B clinical trial sites are in the USA, France, Germany and Spain.

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). An advanced arm of the type B trial is under consideration.

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)

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

Dr Brian Bigger from The University of Manchester has developed a stem cell-based gene therapy for Sanfilippo types A and B, which has been licensed by Orchard Therapeutics. The type A therapy is currently in a clinical trial and type B is in the pipeline. Currently, we don't know if or when trials will start for type B.

This "autologous ex-vivo gene therapy" therapy works by taking the patient's own stem cells (from the blood or bone marrow) and delivering a healthy copy of the faulty gene (SGSH for Type A or NAGLU for Type B) using a virus. 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.

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 Sanfilippo Type A trial at Royal Manchester Children's Hospital. For more information, please read the summary on clinicaltrials.gov.

Enzyme replacement therapy clinical trials

Allievex (formerly Biomarin) ERT for Sanfilippo Type B

Allievex is conducting clinical trials of an enzyme replacement therapy (ERT) for Sanfilippo Type B with sites in Germany, Spain, Taiwan, Turkey, USA and the UK.

The early trials of the ERT called “BMN-250” were conducted by Biomarin, but in October 2019 a licencing deal was made with a newly-formed biotechnology company, Allievex Corporation and the therapy was renamed "Tralesinidase Alfa”.

This ERT is administered weekly directly into the cerebrospinal fluid of the brain (ICV) via a port implanted under the scalp. In February 2018 Dr Nicole Muschol from Germany presented preliminary results of the trial at the WORLD Symposium. She reported that six children had been treated in the trial at different dose levels.

Heparan sulfate was shown to decrease into the normal range in the cerebrospinal fluid and participants’ livers reduced to normal size. At the highest dose there was indication of stabilisation of cognitive ability, but it is still early days and further evidence will need to be gathered to prove the benefit of this therapy. The treatment was generally well tolerated but there were some side effects, mostly due to the invasive way that the therapy is delivered.

The full clinical trial results have not been presented but Allievex is preparing to go to the FDA for drug approval.

More information about the trial.

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:

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'.

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

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.

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 IIIB, the enzyme that needs to be replaced is called alpha-N-acetylglucosaminidase.

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 IIIB, the gene involved is called *NAGLU*.

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.