Clinical Trial Information for Sanfilippo Syndrome Type B

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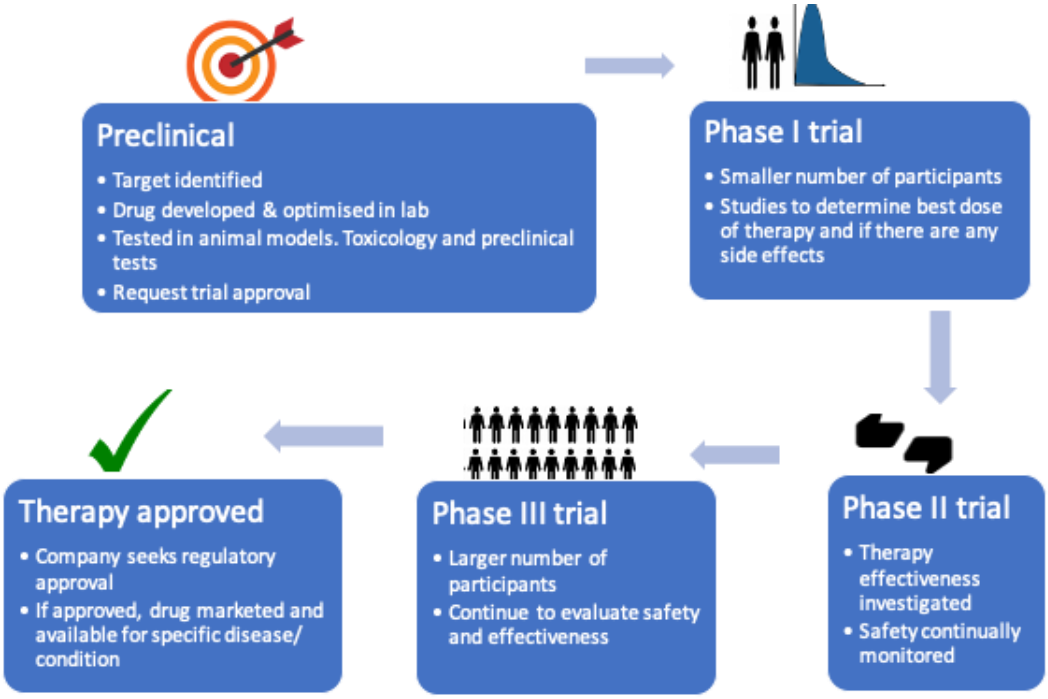
Sanfilippo Children's Foundation

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 have been treated so far, predominantly under the age of 2 years. Reduced heparan sulfate in the urine and CSF has been reported. While no serious adverse events have occurred, one patient has shown an immune response that resolved after 18 months. Full information on cognitive function is not yet available.	Active, not recruiting
Allievex (formerly Biomarin)	Type B trial with Tralesinidase Alfa Phase 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**: Up to 18 years old. Participants must have completed 48 weeks in Part 2 of Allievex's phase I/II ERT and enrol into this study within 8 weeks of completion. **Exclusion**: Current participation in another MPS IIIB clinical trial. A	22 Sanfilippo patients have received treatment at different dose levels. Heparan sulfate decreased in the CSF to normal levels, and livers reduced to normal size. 40% of the rapidly progressing individuals showed a stabilisation or improvement of cognitive development, with particularly	Active, not recruiting

					history of poorly controlled seizures. Has both a cognitive AEq score ≤ 18 months, and a DQ score ≤ 20.	encouraging signs in younger children. Side effects were noted due to the delivery site 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.	Update from 2021 WORLDSymosium: Recruitment and data analysis are ongoing, but initial results with 8 patients (either type A or B) are encouraging. Parent-reported measures of symptoms such as movement, fatigue, behaviour, pain or parental stress are indicating improvements. Further follow-up is required to confirm results.	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 November 2021

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 size of both the liver and spleen, which are enlarged in children with Sanfilippo, has reduced.

Nine patients with Sanfilippo type B and 20 with type A have been treated so far.

During the 2021 WORLD Symposium, Abeona provided an update on the interim trial results to date. The type B gene therapy has predominantly been delivered to children under the age of 2 years. Normalisation of heparan sulphate levels have been seen in all patients treated. While no serious adverse events have occurred, one patient has shown an immune response to the gene therapy that had resolved after 18 months. No treatment effect on cognition has been seen in the cohort treated with the lowest dose. Longer follow-up of patients given a higher dose is required before any further results can be released. Results from the type A trials are also indicating that younger children are responding better in terms of a more typical cognitive development (more details in the Type A trials information sheet).

As a result, 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 arm of the type B trial for more advanced patients 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 and his colleagues from The University of Manchester have 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 (no information on start date available as yet).

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 since launched a full Sanfilippo type A trial at Royal Manchester Children’s Hospital, with three patients aged under 2 years treated to date. Initial results presented at the 2021 WORLD conference indicate that the treatment has been well-tolerated, high levels of enzyme is present in the blood and GAGs (heparan sulphate and other complex molecules) in the urine fell to normal levels. Data on cognitive development is still to come. For more information on this type A trial, 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 directly into the cerebrospinal fluid of the brain (ICV) via a port implanted under the scalp. At the 2021 WORLD conference, Allievex reported that 22 individuals with either rapidly or slowly progressing Sanfilippo type B have been treated bi-weekly with Tralesinidase to date. The treatment has been well tolerated with no serious adverse events. Follow-up and analysis of other outcome measures is ongoing. So far they have shown that HS in the cerebrospinal fluid and liver size are quickly reduced to normal levels. The loss of grey matter volume in the brain was also slowed down over the course of 2 to 3 years compared to that seen in untreated children with Sanfilippo type B. 40% of the rapidly progressing individuals also showed a stabilisation or improvement of cognitive development which was more pronounced in the patients who were younger at the start of treatment. It is too early to tell whether the slowly progressing patients had stabilisation of cognitive development. Interestingly, the researchers also found that hearing impairment was stabilised or improved in a substantial number of the individuals.

The full clinical trial results have not yet been presented but Allievex has indicated that it is making preparations to seek FDA approval for the treatment.

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. It is thought that Anakinra could target the inflammation in the brain which is common across all types of Sanfilippo. A phase II/III trial is currently underway, which was developed in collaboration with, and funded by, Cure Sanfilippo Foundation and other community stakeholders. It aims to assess whether Anakinra can improve the behavioural and other physical symptoms of Sanfilippo. Recruitment and data analysis are still ongoing, but so far the trial has treated 8 patients with either Sanfilippo type A or B. It is showing encouraging signs with most parents reporting improvements in one or more symptoms, such as movement, fatigue, behaviour, pain or parental stress. Longer follow-up and more detailed statistical analysis of the data is still required to determine if the treatment is having a significant effect on symptoms. This drug is approved for the treatment of rheumatoid arthritis (RA). There is a very wide inclusion criteria for this trial – all ages, types and attenuated patients are able to participate (please note that the trial is active but not currently recruiting). More information about this trial is available on its clinicaltrials.gov page.
- 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 is currently being negotiated with the FDA and EU.

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.