Clinical Trial Information for Sanfilippo syndrome

Current as of July 2024

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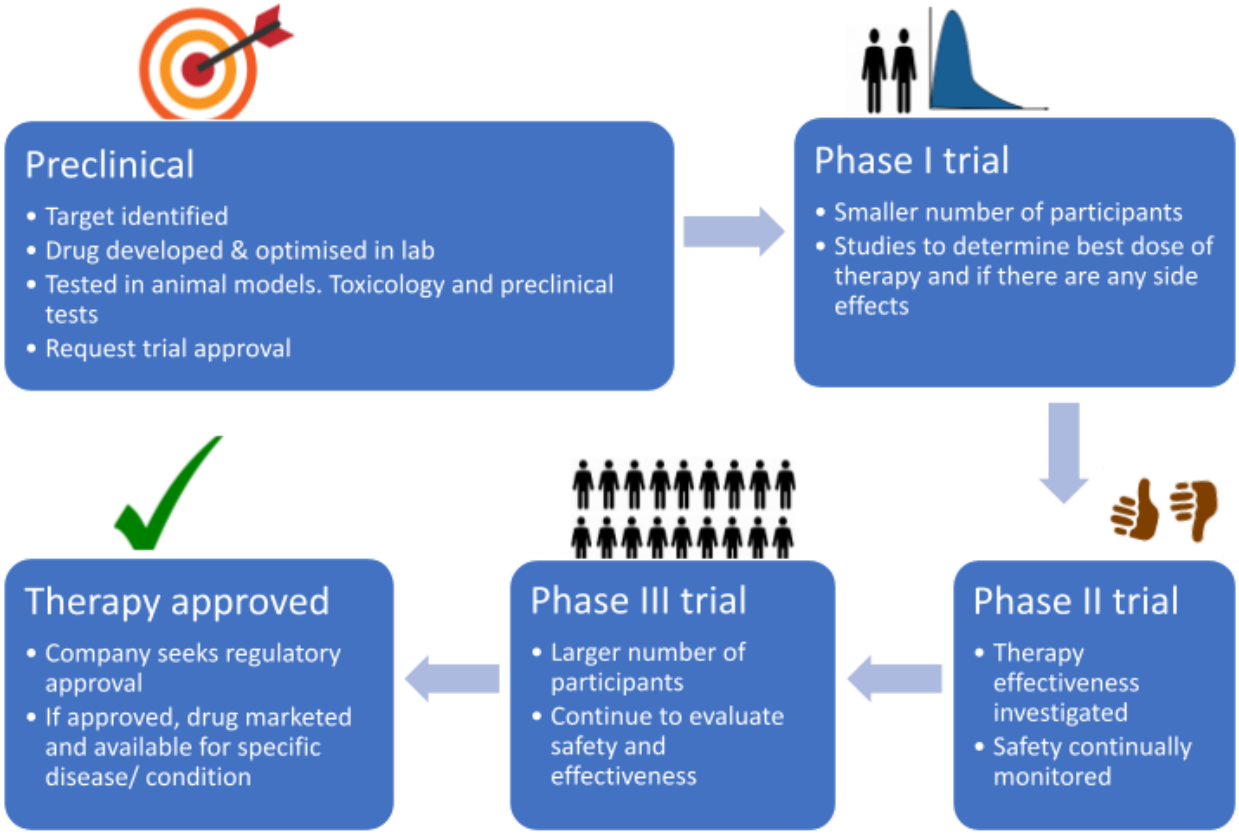
Sanfilippo Children's Foundation

Introduction

The aim of an interventional clinical trial is to determine whether a potential treatment is safe and that it works. Clinical trials involving rare diseases may be run differently from 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 the common phases of the typical drug development and clinical trial process:



Some criteria must be fulfilled for a person to be included in a clinical trial (eligibility or inclusion criteria). There may also be criteria that exclude someone from participating (exclusion criteria). These strict criteria are chosen by the company carrying out the trial and their clinical advisors and in consultation with regulatory authorities to protect the safety of the trial participants and to give the trial the best chance of demonstrating if a therapy works.
A carefully designed clinical trial that proves a therapy to be safe and effective offers the best chance of getting regulatory approval and allowing more patients to access the therapy.

Participating in a clinical trial is not a guarantee of a benefit for the patient, as not all therapies are proven to be safe and effective. However, clinical trials currently provide the only way to access potential treatments for individuals with Sanfilippo syndrome.

This document contains information on the current interventional clinical trials for Sanfilippo syndrome, planned and previous trials. The information for each trial is summarised briefly followed by more information and trial progress updates where they are available. *Please note that not all inclusion or exclusion criteria for a trial may be included here - full eligibility criteria are listed on a clinical trial's official page (links in the document)*. A glossary of some medical terms is provided at the end. If you have any questions or would like more information about Sanfilippo and/or clinical trials, please contact the foundation at research@sanfilippo.org.au.

Clinical trial plans for multiple Sanfilippo subtypes

Lundquist Institute for Biomedical Innovation	TBD	Pending	To be confirmed (but likely multiple subtypes)

Plans for a clinical trial to further investigate the anti-inflammatory drug Anakinra

***Inclusion*: Pending.**
***Exclusion*: Pending.**

Following the completion of a small phase II/III trial (see below), it is possible the Lundquist Institute may consider conducting a larger, confirmatory trial of the anti-inflammatory drug Anakinra, however there have been no recent updates on this.

Anakinra may target the inflammation in the brain which is common across all types of Sanfilippo. Anakinra is currently used to treat several other diseases, including a childhood CNS autoinflammatory disease. This trial aimed to see if it could be repurposed for Sanfilippo.

There were very wide inclusion criteria for the phase II/III trial – all ages, subtypes of Sanfilippo and attenuated patients could participate – though potential inclusion criteria for a future trial are not yet known.

Results from the initial trial indicated the therapy was safe, with encouraging signs of improvement for parent-reported measurements of behavioural symptoms, sleep, pain, movement disorder, and/or parental stress. More background on why anti-inflammatory therapies may improve symptoms of Sanfilippo can be found on our website.

Amsterdam UMC	Phase III	Planning	A	B	C	D

Plans for a clinical trial of twice daily oral administration of cannabidiol (CBD) in patients who have severe behavioural symptoms.

***Inclusion*: At least 6 years of age and clinically diagnosed with Sanfilippo syndrome, Tuberous Sclerosis Complex, or Fragile X syndrome. Experiencing severe behavioural symptoms (with a minimum score on a psychiatric test).**
***Exclusion*: Hypersensitivity to cannabinoids or other ingredients used in the study, including sesame oil. Significantly impaired liver function. Use of cannabidiol or similar drugs within the previous 2 months, or unwilling to abstain from recreational/medicinal cannabis or similar drugs.**

Amsterdam UMC plans to run a phase III clinical trial testing oral cannabidiol (CBD) twice daily in patients who have severe behavioural symptoms due to one of three conditions, including Sanfilippo syndrome. Participants will be given the drug in their "natural setting" (e.g. at home) instead of having regular hospital visits for drug administration.

The trial primarily aims to test if the treatment with CBD can improve irritability in the study participants. It will measure if there are changes in other behavioural symptoms, including anxiety and hyperactivity, and other outcomes such as seizure frequency and parental stress. A placebo group will be included; however, there will be crossovers, meaning that every patient who enrols in and completes the trial will receive CBD at least once for a period of time. More information about the trial can be found on its EU Clinical Trials Register page.

Current and planned clinical trials for Sanfilippo Type A

Ultragenyx Pharmaceutical Inc.	Phase I/II/III	Active, not recruiting	**A**	B	C	D

Gene Therapy for patients in the early phases of Sanfilippo

***Inclusion*: Up to 2 years of age, or over 2 years with Developmental Quotient (DQ) above 60.**
***Exclusion*: Previous exposure (antibodies) to AAV9 virus. Children with attenuated (slow-progressing) Sanfilippo are ineligible.**

The phase I/II gene therapy trial uses an AAV9 delivery virus now known as UX111 after Ultragenyx Pharmaceutical Inc. took over the trial from Abeona in May 2022. Data reported so far shows encouraging safety results and a reduction in heparan sulfate levels. Cognitive data are encouraging in children treated under the age of two.

This trial commenced in 2016, under Abeona Therapeutics with funding support from international patient groups including the Sanfilippo Children's Foundation. Sites include the USA, Spain, and Australia. Ultragenyx Pharmaceutical Inc. took over the program in May 2022.

The gene therapy is administered intravenously (into the bloodstream), carried by a virus (AAV9) that crosses the blood-brain barrier to deliver healthy copies of the gene to the brain.

As initial results from the trial linked therapy effectiveness to younger age at administration, the inclusion criteria were narrowed to patients aged under 2 years or over 2 years old with a developmental quotient (DQ) of more than 60. This cohort was called the 'modified intention to treat' group (mITT), and 17 children have been treated as part of this group. Children must also test negative on a blood test to detect prior exposure to the AAV9 virus. AAV9 is a harmless common virus, but antibodies to the virus can limit the therapy's efficacy.

The latest data show heparan sulfate levels reduced in the CSF within one month of treatment in all 17 mITT patients, with levels reduced by an average of 63% in the follow-up period to August 2023 (ranging between 11.3-60 months post-treatment). At this time point, cognitive testing also indicated improvements or stability in 16 of the 17 patients compared to untreated children who would typically decline. There was a strong correlation between overall reductions in heparan sulfate levels over time in the CSF and higher cognitive scores, with 15 of 17 patients having both a reduction in CSF heparan sulfate and an improvement in cognitive function.

Ultragenyx has indicated that they will continue with the long-term follow-up of the patients who received UX111 whilst also working towards a submission to the USA Food and Drug Administration (FDA) for marketing approval. In June 2024, they were given the green light to apply to the FDA for Accelerated Approval for UX111. An Accelerated Approval from the FDA allows a treatment to be used by patients before the full clinical outcomes are known. Instead, the FDA accepted the levels of heparan sulfate in the cerebrospinal fluid (CSF) could be used as a biomarker to support an application from Ultragenyx. This is likely to be submitted in late 2024 or 2025.

A separate trial of the same treatment in older and more advanced patients with Sanfilippo type A was terminated in March 2022. This trial included patients aged 2-18 years with a Cognitive Developmental Quotient (DQ) less than 60. Unfortunately, no improvements were seen in participants' neurocognitive function, and the potential risks from the therapy were deemed higher than the likely benefits to patients with advanced disease. The patients treated in this trial are continuing to have annual safety monitoring with their local physicians.

Esteve	Phase I/II	Status unknown	**A**	B	C	D
	Gene Therapy via single injection into the CSF fluid-filled spaces of the brain					

***Inclusion*: 2 years and older with Sanfilippo type A. Onset of symptoms within the first 6 years of life. Potential 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.**

The phase I/II trial based in Barcelona, uses an AAV9-CAG-coh-SGSH gene therapy, administered via a single intracerebro-ventricular (ICV) injection. The trial is listed as ongoing but no updates or results have been released.

Esteve indicated a plan to recruit six patients for this initial clinical trial. The trial was first listed on the EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) in February 2016 with an anticipated duration of 5 years.

For more information, visit Esteve's pipeline and the European Clinical Trials Register.

Orchard Therapeutics	Phase I/II	Active, not recruiting	**A**	B	C	D
	Gene Therapy using the patient's stem cells that are treated and transplanted back into the patient					

***Inclusion*: 3-24 months of age with Sanfilippo type A. Normal cognitive function or only mild deterioration. Indications of rapidly progressing disease.**
***Exclusion*: Current/previous participation in a gene/cell/enzyme replacement therapy trial.**

The phase I/II trial of autologous ex-vivo gene therapy involves the collection of bone marrow cells from the patient, which are treated with gene therapy and then transplanted back. Five Sanfilippo type A children aged under 2 years have been treated to date, with early results indicating promising gains in cognitive skills in four patients.

Bone marrow transplants (without gene therapy) have been previously tried as a treatment for Sanfilippo, but were largely unsuccessful because the cells did not produce enough of the enzyme. This ex-vivo gene therapy 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.

This therapy called "autologous ex-vivo gene therapy" was developed by Dr Brian Bigger and colleagues from The University of Manchester for Sanfilippo types A and B. The University of Manchester entered into a licensing agreement with Orchard Therapeutics, now a Kyowa Kirin

company, to bring its Sanfilippo type A stem cell gene therapy program to human clinical trial. A 30-month-old boy with Sanfilippo Type A received this experimental therapy in 2019, under a "Special Access" licence. This child showed a reduction of storage molecules in urine, blood and CSF, and a stabilisation of cognitive skills.

Orchard Therapeutics then launched a full trial at Royal Manchester Children's Hospital. Five patients between 3-24 months of age with severe Sanfilippo Type A have been treated to date. The therapy (called OTL-201) has been well-tolerated and the cells have been incorporated well following transplantation. Side effects reported to date are those commonly seen after a stem cell transplant. In treated patients, SGSH enzyme activity levels are 25-30 times higher than normal. Heparan sulfate storage rapidly reduced in the blood and urine by 80-90% and substantially reduced in the CSF.

Early data indicate that cognitive skills gained by four of the five study participants treated with OTL-201 are in line with development in healthy children, and they do not display the typical behavioural symptoms of Sanfilippo. All patients must be followed for a longer period post-treatment before any firm conclusions can be drawn.

The licence for the Sanfilippo type B therapy has been returned to Manchester University and may be developed separately by the research team there.

For more information on the clinical trial, please read the summary on clinicaltrials.gov.

***Inclusion*: 1-18 years of age with Sanfilippo type A, with body weight 10 kg or more.**
***Exclusion*: Previous participation in a gene therapy or cell therapy trial with successful engraftment, or the current/previous use of an investigational product or other particular products within specified timeframes.**

Japanese company, JCR Pharmaceuticals, have commenced a phase I/II clinical trial of their product JR-441 in patients with Sanfilippo type A. The enzyme replacement therapy is engineered to cross the blood-brain barrier and administered via weekly intravenous injection. The first patient was dosed in Germany as announced in October 2023.

JR-441 is an enzyme replacement therapy (ERT) engineered to cross the blood-brain barrier to deliver the sulfamidase enzyme to the brain. It can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo with less potential for side effects as seen with direct injection into the CNS.

Data from Sanfilippo animal models showed that intravenous injection of JR-441 increased enzyme levels in the brain and reduced heparan sulfate to near-normal levels. JR-441 received an orphan drug designation from the European Commission in January 2022 and the USA's FDA in December 2023. You can also read more on our website. A similar drug, JR-141, is now approved in Japan to treat Hunter Syndrome, a form of mucopolysaccharidosis (MPS) like Sanfilippo.

JCR Pharmaceuticals is also planning a phase I/II clinical trial to investigate their ERT for patients with Sanfilippo type B (see below). For more information on the clinical trial for Sanfilippo type A, see the summary on clinicaltrials.gov.

***Inclusion*: All participants must be 2-18 years old with Sanfilippo type A.**
***Exclusion*: Presence of unstable/poorly controlled medical condition(s) in addition to Sanfilippo diagnosis that may cause safety concerns or affect study results. Lost the ability to walk independently, in the opinion of the investigator. Previous participation in a gene therapy or cell therapy trial, or the current/previous use of an investigational product or other particular products within specified timeframes.**

Denali Therapeutics has commenced recruitment for a phase I/II clinical trial for their enzyme replacement therapy candidate, DNL126, in patients with Sanfilippo type A. DNL126 has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain. It can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo without the side effects commonly seen from direct injection into the CNS.

In early June 2024, the USA's Food and Drug Administration (FDA) selected Denali Therapeutic's DNL126 for the START pilot program, which is intended to increase the frequency and timeliness of a company's communications with the FDA to help improve the efficiency of a drug development program.

The study aims to evaluate the best dose of DNL126 and its safety with a small number of participants. This initial clinical trial currently has sites in the USA.

For more information, see the ClinicalTrials.gov entry for the study or contact the patient advocacy team at Denali via patients@dnli.com.

***Inclusion*: Pending.**
***Exclusion*: Pending.**

GC Biopharma Corp. is a biotechnology company based in South Korea. They have an enzyme replacement therapy candidate called GC1130A for Sanfilippo type A, developed in collaboration with Novel Pharma. The ERT is to be delivered via intracerebroventricular (ICV) injection.

In January 2024, the company announced that the European Medicines Agency (EMA) had granted an Orphan Drug Designation (ODD) to GC1130A, which followed an ODD from the U.S. FDA in January 2023.

In June 2024, GC Biopharma and Novel Pharma received an FDA FastTrack designation for GC1130A. FastTrack designation means that the FDA will speed up the review of important stages in the clinical development of a therapy to get new therapies to patients faster. GC Biopharma and Novel Pharma plan to start a phase I clinical trial with initial trial sites in Japan, Korea and the USA.

Current and planned clinical trials for Sanfilippo Type B

***Inclusion*: Less than 18 years of age with a confirmed diagnosis of Sanfilippo type B.**
***Exclusion*: Prior treatment with a gene therapy or stem cell transplant with successful engraftment. Current/previous use of an investigational product or other particular products within specified timeframes.**

Japanese company, JCR Pharmaceuticals, plans to start a phase I/II clinical trial to investigate their enzyme replacement therapy (ERT) candidate JR-446 for patients with Sanfilippo type B.

In September 2023, it was announced that JCR would partner with Medipal Holdings to progress the development of the Type B program, and in July 2024, they announced approval from Japan's regulatory authority to commence the clinical trial, which they hope to start in 2024.

JR-446 is an ERT that has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain. It can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo without the side effects commonly seen from direct injection into the CNS. Data from Sanfilippo types A and B animal models showed that intravenous injection of the ERT increased enzyme levels in the brain and reduced heparan sulfate to near-normal levels.

A similar drug, JR-141, is now approved in Japan to treat Hunter Syndrome, a form of mucopolysaccharidosis (MPS) like Sanfilippo. JCR Pharmaceuticals has an ERT for Sanfilippo type A, called JR-441, currently in phase I/II clinical trial (see above).

For more information, see the ClinicalTrials.gov entry for the study.

***Inclusion*: Pending.**
***Exclusion*: Pending.**

Denali Therapeutics has an enzyme replacement therapy for Sanfilippo type B in its pipeline and plans to prepare for a clinical trial in the future.

Their ERT technology has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain. It can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo without the side effects commonly seen from direct injection into the CNS.

Denali Therapeutics is also using its ERT technology in a phase I/II clinical trial for Sanfilippo type A, which is currently recruiting participants at two sites in the USA (see above).

Clinical trial plans for Sanfilippo Type C

***Inclusion*: Pending.**
***Exclusion*: Pending.**

In November 2018, Phoenix Nest Inc. acquired the rights to a Sanfilippo type C gene therapy developed by Dr Brian Bigger at the University of Manchester. The approach uses an AAV vector to deliver a healthy copy of the *Hgsnat* gene.

Pre-clinical development is continuing. In preparation for a clinical trial, Phoenix Nest Inc. is sponsoring a Natural History study to collect observational data from patients with Sanfilippo type C and their caregivers. The study is not yet recruiting but plans to have a site in France with some parts of the study also open to overseas participants. More information on the Natural History study can be found on its ClinicalTrials.gov page.

Clinical trial plans for Sanfilippo Type D

***Inclusion*: Pending.**
***Exclusion*: Pending.**

Phoenix Nest Inc. has licensed an enzyme replacement therapy (ERT) from Dr Patricia Dickson, a clinician-researcher from Washington University School of Medicine in St. Louis. This therapy is designed to deliver the enzyme missing in Sanfilippo Type D, called GNS, intrathecally (into the spinal fluid).

Dr Patricia Dickson and her collaborators at The Lundquist Institute (formerly LA BioMed) developed the potential treatment, which shows promise in a Type D animal model. In 2018, the team received a grant from the National Institutes of Health (NIH), USA, to make large quantities of the enzyme and test its safety in animal models.

In late 2021, Phoenix Nest received NIH funding to undertake a Natural History study for Sanfilippo type D. Data will be collected from living and deceased type D patients worldwide and will provide information on disease symptoms and trajectory that can be used for

comparison in future clinical trials when testing therapies. More information on the study, including contact information for families and physicians, can be found in the media release from Phoenix Nest Inc.

Other therapies in pre-clinical development

Researchers are working to find other drugs that may reduce the progression of Sanfilippo and improve quality of life. These include

- Substrate reduction therapies (SRT) to reduce the amount of heparin sulfate that is produced by the body so that there is less to build up. Learn more here.
- Chaperones that help the faulty enzymes fold correctly and get to the right part of the cell (the lysosome) to do their job of breaking down heparan sulfate. More informaiton here.
- 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 (see active Anakinra study above and our website article)
- 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.

Completed and terminated clinical trials for Sanfilippo

Lundquist Institute for Biomedical Innovation	Phase II/III	Completed	A	B	C	D

Anti-inflammatory therapy using Anakinra via daily injection

Inclusion: *Ages 4+. All sub-types of Sanfilippo syndrome including attenuated patients.*
Exclusion: *Current participation in another clinical trial. Previous or current treatment with specific anti-inflammatory drugs. Severe liver or kidney impairment.*

The phase II/III trial involved the daily subcutaneous injection of the anti-inflammatory drug Anakinra. Anakinra has previously been approved for the treatment of several diseases, including a CNS autoinflammatory disease that occurs in children. Twenty-four patients with Sanfilippo were recruited for the study. There were encouraging signs of improvements in some symptoms, including parent-reported measurements of sleep, pain, movement disorder, and parental fatigue.

The study investigators are considering a larger follow-up trial to confirm these results.

More background on why anti-inflammatory therapies may improve symptoms of Sanfilippo can be found on our website.

Manchester University NHS Foundation Trust	Phase III	Terminated	A	B	C	D

Substrate Reduction Therapy using high dose oral Genistein Aglycone

Inclusion*: Aged 2-15 years with a confirmed diagnosis and clinical symptoms of Sanfilippo type A, B, or C. Able to walk unaided.*
Exclusion*: Previous haematopoietic stem cell transplantation or use of genistein or any other investigational therapy for Sanfilippo. Known adverse reaction to genistein.*

From 2014 to 2018, the Phase III clinical trial was undertaken to test the safety and effectiveness of the promising oral SRT candidate, Genistein Aglycone. The therapy was administered daily to patients with Sanfilippo types A, B, or C.

At 12 months post-treatment-initiation, heparan sulfate in the CSF was slightly lower in the treated cohort. However, there was no significant improvement between the treated and untreated groups in terms of Developmental Quotient at 12 months. No clinically meaningful benefit was seen in the neuropsychological tests of the 21 children who took part, and investigations were discontinued.

The trial was terminated in June 2018 due to the shelf-life expiry of the product.

***Inclusion**: 6 months and older with Sanfilippo type A. Developmental Quotient (DQ) greater than 60.*
***Exclusion**: Participation in another gene or cell therapy trial. Past use of enzyme replacement therapy for 3 months or more. Children with attenuated (slowly progressing) forms of Sanfilippo are unable to take part.*

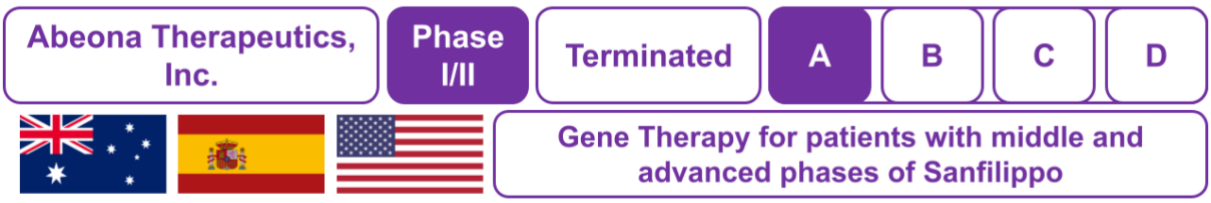
Lysogene was founded by Karen Aiach, mother of a child with Sanfilippo Type A in France. In 2013, Lysogene completed a Phase I/II clinical trial for its gene therapy product SAF-301, in which four children with Sanfilippo Type A were treated. The gene therapy - an AAVrh10 virus carrying a healthy copy of the SGSH gene - was directly injected 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 was conducted with sites in the USA, France, UK, Germany, and the Netherlands.

In June 2020, with 19 patients enrolled, recruitment was put on hold by the FDA due to unusual MRI findings of brain white matter change at the sites of therapy injection. Lysogene later confirmed that no clinical symptoms were associated with these MRI findings and they had stabilised or decreased after 12 months in all patients. It is thought the lesions represent areas of very high enzyme activity with a full depletion of heparan sulfate. One patient in the trial died at age 5 but the treatment was not implicated in their death.

Results provided at ADVANCE 2023 indicate an approximately 20% reduction in heparan sulfate in the CSF of patients, which was sustained for at least 24 months following treatment. Heparan sulfate levels in the bloodstream remained unchanged. The levels of a protein called neurofilament light (NfL) were on average 41% lower in the CSF 24 months post-treatment compared to pre-treatment levels; this protein is only released from damaged neurons and is a marker of ongoing brain damage. Patients treated at 30 months of age or below, even those with genetic changes associated with severe disease, have had a stabilisation or continuing development of cognitive, language and motor functions. Two of these patients have achieved higher developmental milestones than previously seen in untreated children. Patients treated above 30 months of age showed no improvement in cognitive development. The team hope to publish the full trial results when they can.

In 2023, with no financial support, Lysogene announced judicial liquidation and its delisting. At this time, the future of SAF-301 remains unknown. A longer follow-up of patients is required, particularly of the younger patients in the study. As noted at ADVANCE 2023, patient follow-up may be possible with NGO funding.



***Inclusion**: Aged 2 to 18 yrs. Participants must have a Cognitive Developmental Quotient (DQ) of 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 (slowly progressing) forms of Sanfilippo are unable to take part.*

The gene therapy trial involved a single intravenous injection of the gene *SGSH* carried by the AAV9 virus. Enrolment commenced in late Oct 2019; however, the trial was terminated in April 2022 as no improvement was seen in the patients with advanced disease. Abeona has confirmed that all patients will receive an annual follow-up up to 5 years post-injection for safety.

A trial using the same gene therapy involving younger patients in the early phase of the disease is ongoing (details available above).

For the initial phase I/II trial for patients 3+ years of age:
***Inclusion**: Aged 3 years or older, with a developmental age of at least 1 year.*
***Exclusion**: MPS IIIA behavioural-related issues that would interfere with developmental tests. Spinal issues that wouldn't allow the surgical implantation of the IDDD.*
An extension study was run for this trial.

For the initial phase II trial for patients 1-2 years of age:

***Inclusion**: Aged 1-2 years, with a Cognitive Developmental Quotient (DQ) score ≥60%.*

***Exclusion**: MPS IIIA behavioural-related issues that would interfere with developmental tests. Spinal issues that wouldn't allow the surgical implantation of the IDDD. Children with attenuated (slowly progressing) forms of Sanfilippo are unable to take part.*
An extension study was also run for this trial.

The enzyme was delivered via an intrathecal drug delivery device (IDDD) implanted under general anaesthesia into the spinal column of patients for regular ERT administration into the spinal fluid.

The initial trial enrolled 12 participants aged over 3 years from 2010-2012, with ERT administered over 6 months. Ten of these participants then completed an extension study. The ERT drug was well-tolerated by patients, but the delivery device caused some mild to moderate adverse events and failed in 5 patients. Across both the initial trial and the extension study, patients' average HS levels were reduced in the CSF.

However, cognitive assessments at 54 months indicated a continued cognitive decline. Patients also showed decreased brain volume over this time. The extension study was discontinued due to a lack of efficacy.

A separate study with the same ERT in younger individuals aged 12-48 months also proved ineffective. However, a small number of patients were described as 'responders', who experienced a slower rate of cognitive decline.

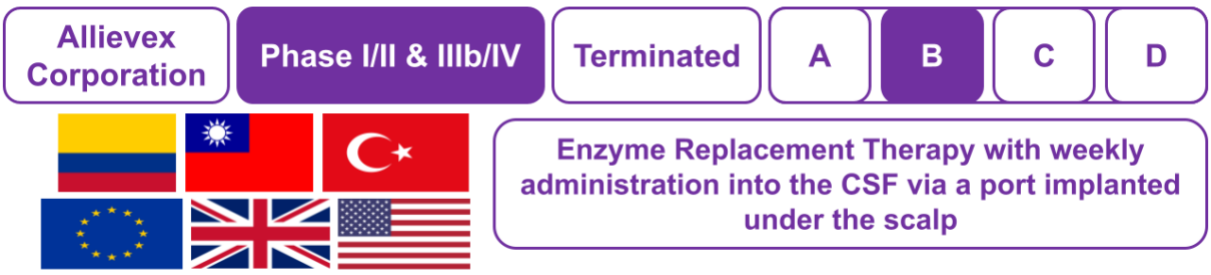
All studies by Shire involving MPS III have been completed or were terminated by April 2019.

***Inclusion**: Between 1-6 years of 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).*

Sponsored by Swedish Orphan Biovitrum (SOBI), an initial phase I/II trial commenced in June 2018 and treated six patients with Sanfilippo type A via weekly intravenous injection. This was followed by an extension study around a year later, with the same six patients as they continued to receive the therapy with a potentially higher dose.

Six children received treatment in the trial, aged 15-65 months at the time of their first dose. Reduced heparan sulfate was seen in CSF (79% reduction after 2 years of treatment), and also blood and urine. The low patient number makes it difficult to determine the effect on cognition, but overall results indicate a stabilisation of cognitive development in the younger patients.

SOBI concluded the trial in April 2021. Results were published in July 2022 - read more here.



***Inclusion**: Must have completed 48 weeks in Part 2 of Allievex's Phase I/II trial and enter this Phase II trial within 8 weeks. Ages up to 18 years. Must be able to undertake study procedures and evaluations (e.g. neurosurgery, MRIs, cognitive testing).*
***Exclusion**: Current participation in another MPS IIIB clinical trial. A history of poorly controlled seizures.*

The early trials of the enzyme replacement therapy (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 (AX 250).

The phase I/II trial for patients with Sanfilippo type B involved weekly administration of the ERT into the CSF via a port implanted under the scalp. After one year of treatment, administration frequency was reduced to once every other week. The phase I/II trial locations included Columbia, Germany, Spain, Taiwan, Turkey, the USA, and the UK, and 23 patients were treated.

Data from the study indicates heparan sulfate levels reduced to normal in the CSF and blood, and liver size reduced to normal. The loss of grey matter volume in the brain slowed and was preserved over 2-3 years in many patients compared to that seen in untreated children with Sanfilippo type B. The data indicates that preserved grey matter volume correlates with preserved cognition, and indicates likely benefit over time with AX 250 treatment. The most promising results were seen in the youngest patient, who began treatment at around 2 years of age. The treatment was well tolerated with no serious adverse events. Side effects were related to the delivery mechanism. Patients continue to be monitored via a phase IIIb/IV clinical trial.

At ADVANCE 2023, Allievex noted that they have approached drug regulatory bodies for accelerated approval of AX 250. For over two years, Allievex negiotated with the FDA, which initially requested a confirmatory placebo-controlled study. This left the company in a situation where it struggled to raise the necessary capital (tens of millions of dollars) to fund a new trial or to be acquired.

Allievex met with the FDA in March 2024 following much advocacy by them and others, particularly regarding the use of heparan sulfate as a surrogate biomarker for accelerated approvals of therapies for Sanfilippo and other neuronopathic MPS disorders. While the FDA encouraged Allievex to file for accelerated approval of AX 250 at this meeting, the company was unable to raise the necessary capital or be acquired in this time and announced commencement of formal liquidation proceedings in July 2024.

More information on the early clinical trial data released in November 2022 can be found on our website.

***Inclusion**: Between 2 and 12 years of age, and with documented developmental delay.*
***Exclusion**: Prior gene therapy, hematopoietic stem cell or bone marrow transplant. Egg allergy.*

Two trials were run by Alexion: a trial for type B patients 2-12 years (Phase I/II), and a trial for patients 5+ years (Phase I/II). Both involved bi-weekly intravenous injection of SBC-103 ERT.

For the type B trial for patients 2-12 years, 11 patients between 2-10 years of age were recruited. Patients received escalating doses of the ERT via intravenous infusion for around two years. Although the ERT treatment itself was well-tolerated, there was no clear evidence that the SBC-103 offered clinically meaningful neurocognitive benefits. In February 2017, Alexion decided to discontinue investigations into SBC-103.

All studies by Alexion involving MPS III were completed or terminated by 2017.

***Inclusion**: Age 6 months to approx with Sanfilippo type B. 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 (slowly progressing) forms of Sanfilippo are unable to take part.*

The Phase I/II Transpher B Study involved a single intravenous injection of gene therapy using the AAV9 virus.

11 Sanfilippo Type B patients were treated, predominantly under the age of 2 years. Reduced heparan sulfate in the urine and CSF was reported. While no serious adverse events occurred, one patient showed an immune response that resolved after 18 months. Full information on cognitive function was not provided. Abeona discontinued the trial in April 2022.

***Inclusion**: Age 18 months to 60 months with Sanfilippo type B. Patient affiliated to/covered by a French social security regimen or European Health Insurance Card.*
***Exclusion**: Presence of brain atrophy on baseline MRI. Patients unable to walk independently. Patients who have had medication to modify the natural course of MPS IIIB in the prior 6 months before vector injection (excluding any sleep and mood regulators).*

The Phase I/II type B trial using rAAV2/5-hNAGLU was delivered via a single intraparenchymal injection, which involved surgery to inject the therapy directly into different parts of the brain.

The study ran from 2013 to 2019 in Paris, with four children treated at 20, 26, 30 and 53 months of age. 5.5-year follow-up results showed no serious adverse events attributed to the gene therapy, along with sustained enzyme production of the type B enzyme (NAGLU) in the CSF of all patients.

On average, NAGLU levels were between 14-24% of that found in children without Sanfilippo. Neurocognitive assessments after 5.5 years suggested that 3 of the 4 patients did not benefit from the treatment, and had atrophy (shrinkage) of the brain. The youngest patient may have received some benefit in terms of cognition.

UniQure completed the trial in November 2019.

There are currently no completed or terminated Sanfilippo Type C-only or Type D-only interventional clinical trials.

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 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 physically protect the brain and spinal cord, 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. The enzyme is sulfamidase (type A); NAGLU (type B); HGSNAT (type C); or GNS (type D).

Gene Therapy
Gene Therapy involves the delivery of a healthy copy of a gene into the body. The four subtypes of Sanfilippo are caused by four different genes. The gene is called *SGSH* (type A); *NAGLU* (type B); *HGSNAT* (type C); or *GNS* (type D).

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.

Interventional clinical trials involve the use of a treatment, for example, a drug or a gene or enzyme replacement therapy, to see if the treatment is safe and can benefit a population. This is in contrast to observational clinical trials, which include Natural History studies, that aim to observe the natural course of a disease without the use of a treatment.

Intrathecal injection
An intracerebral injection is an injection into the spinal cavity, in the space around the spinal cord (which is bathed in cerebrospinal fluid (CSF)). This is a way to deliver drugs to the central nervous system that may be unable to cross the blood-brain barrier.

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 (ICV) 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.

Intraparenchymal injection
An intraparenchymal injection is an injection directly into the brain's functional tissue, known as the brain parenchyma. This administration method delivers 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 so that the therapy is delivered via the bloodstream. 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 setups. 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. They 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') and can 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. 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 that 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.