Clinical Trial Information for Sanfilippo syndrome

Current as of August 2022

Contents

Introduction .................................................................................................................. 2
Current clinical trials involving multiple Sanfilippo subtypes .............................. 2
Current and planned clinical trials for Sanfilippo Type A .................................. 4
Current and planned clinical trials for Sanfilippo Type B .................................. 8
Clinical Trial Plans for Sanfilippo Type C .............................................................. 10
Clinical Trial Plans for Sanfilippo Type D .............................................................. 11
Other therapies in pre-clinical development ......................................................... 11
Completed and terminated clinical trials for Sanfilippo .................................. 12
Glossary ...................................................................................................................... 16
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 the common phases of the typical drug development and clinical trials process:

There are criteria that must be fulfilled for a person to be included in a clinical trial. There may also be criteria that exclude someone from participating. These strict criteria are chosen by the company carrying out the trial and their clinical advisors 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 at getting regulatory approval and allowing more patients to access it.

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 clinical trials for Sanfilippo syndrome, as well as both 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 is 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.
Current clinical trials involving multiple Sanfilippo subtypes

**Lundquist Institute for Biomedical Innovation**

**Phase II/III**

**Active, not recruiting**

**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 I/II trial involves the subcutaneous injection of the anti-inflammatory drug Anakinra once a day. Recruitment and data analysis are ongoing. Some improvements have been suggested in parent-reported measures of symptoms.

Anakinra, a drug that suppresses inflammation, is in a 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. Anakinra has previously been approved and is in use for the treatment of several diseases, including a CNS autoinflammatory disease that occurs in children.

A phase II/III trial is currently underway, which was developed in collaboration with, and funded by, Cure Sanfilippo Foundation (USA) and other community stakeholders. It aims to assess whether Anakinra can improve the behavioural and other physical symptoms of Sanfilippo.

Data analysis is still ongoing, but so far the trial has treated 21 patients with either Sanfilippo type A or B at various ages and stages of disease progression. Parent-reported measurements of symptoms are indicating all participants had stable or improved symptoms in one or more of sleep, pain, parental fatigue and movement disorder. Clinical outcome measures, which are measured by clinicians, indicate there has been no worsening overall and possibly a slight improvement across the 36 weeks analysed so far. Longer follow-up and statistical analysis of the data are still required to determine if the treatment is having a significant effect on symptoms. It is likely that a larger trial will be needed to confirm any findings from this study.

There is a very wide inclusion criteria for this trial – all ages, types and attenuated patients are able to participate. The trial is active (still underway) but not currently recruiting. More information about this trial can be found on its [clinicaltrials.gov page](https://clinicaltrials.gov).

More background on why anti-inflammatory therapies may improve Sanfilippo symptoms can be found [on our website](https://www.curesanfilippo.org).
Current and planned clinical trials for Sanfilippo Type A

**Inclusion:** Age 6 months to approx. 2 years. Developmental Quotient (DQ) above 60

**Exclusion:** Previous exposure (antibodies) to AAV9 virus (20-30% of children excluded for this reason). Children with attenuated (slow-progressing) Sanfilippo are ineligible.

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

In May 2016, a phase I/II trial of the gene therapy ABO-102 started in the USA, sponsored by Abeona Therapeutics. The trial involved funding from international patient groups including the Sanfilippo Children's Foundation. Sites include the USA, Spain, and Australia. In May 2022, Ultragenyx Pharmaceutical Inc. announced it will be taking over the ABO-102 gene therapy program now referred to as UX111.

The gene therapy is administered intravenously (into the bloodstream), carried by a virus (AAV9) that crosses the blood-brain barrier to deliver a healthy copy 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 with a developmental quotient (DQ) of more than 60. Children must also test negative on a blood test to detect prior exposure to the AAV9 virus. AAV9 is a harmless virus that exists in the environment, but antibodies to the virus can limit its efficacy. 20-30% of children are excluded for this reason.

Preliminary data indicate sustained reductions in heparan sulfate in the CSF in the 24 months post-injection. Heparan sulfate and other complex storage molecules are reduced in the blood and urine and liver and spleen size is reduced. No serious adverse events have emerged to date. Early data from the measurements of brain volume in MRI scans of younger patients show that the total brain volume is increasing, in contrast to the brain shrinkage seen in untreated children. To date, 22 children aged 0-2 years have been treated.

In early April 2022, Abeona announced that the USA Food & Drug Administration requested that the youngest children in the trial be followed until they reach 5 years of age, before providing a final read-out of the data. This prompted Abeona to seek a commercial partner to take over the program. In May 2022, Ultragenyx acquired the global rights to the therapy.

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. Abeona confirmed that patients would have annual safety monitoring with their local physicians.
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 Sanfillipo are unable to take part.

The phase II/III clinical trial into the gene therapy product LYS-SAF302 uses an AAVrh10 delivery virus administered via a single intra-cerebral injection.

In mid-2020, there were some safety concerns regarding early MRI findings at the injection site, but this was later resolved. Encouraging preliminary cognitive outcomes have been reported in younger patients in July 2022.

Lysogene was founded by Karen Aiach, mother of a child with Sanfilippo Type A in Paris, France. In 2013, Lysogene successfully 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 is underway 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. In a press release, the company said that the 19 patients treated so far would continue to be closely monitored. Since then, Lysogene has confirmed that no clinical symptoms were associated with these MRI findings and they had stabilised or decreased after 12 months in all patients. One patient in the trial died at age 5 but the treatment was not implicated in their death.

The most recent updates indicate an approximately 20% reduction in heparan sulfate in the CSF of patients, which is sustained for at least 24 months following treatment. The levels of a protein called neurofilament light (NfL) was 33% lower in the CSF 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 31 months of age or below, even those with genetic changes associated with severe disease, have had a stabilisation or continuing increase in cognitive, language and motor functions. Two of these patients have achieved higher developmental milestones than previously seen in untreated children. Lysogene have indicated that final results are expected in September 2022.

More details of the trial are available here.
**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** uses an AAV9-CAG-coh-SGSH gene therapy, administered via a single intracerebro-ventricular (ICV) injection. The trial is recruiting and no results have been released yet.

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); this is called an intracerebroventricular (ICV) injection. Esteve plan to recruit six patients for this initial clinical trial. No results from this trial have been released so far.

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 pipeline and the European Clinical Trials Register.

**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 the gene therapy and then transplanted back.

Five Sanfilippo type A children aged under 2 years have been treated to date. There are some indications of lower heparan sulfate levels and symptom improvements.

Dr Brian Bigger and colleagues from The University of Manchester have 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) into the cells. 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. 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 entered into 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 30-month-old boy with Sanfilippo Type A received this experimental therapy in January, 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. It may take longer for the effects to be seen in the brain, due to the longer time needed for the modified stem cells to populate the brain.

The patients will be followed for 3 years and their neurocognitive development compared against the expected development of untreated patients.

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

---

Japanese company, JCR Pharmaceuticals, has plans to prepare for a global clinical trial, potentially starting in 2023, with JR-441 in patients with Sanfilippo type A. JR-441 received an orphan drug designation from the European Commission in January 2022.

JR-441 is an enzyme replacement therapy (ERT) that has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain and can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo more effectively with fewer adverse side effects.

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.

A similar drug, JR-141, is now approved in Japan to treat Hunter Syndrome, a form of mucopolysaccharidosis (MPS) like Sanfilippo. More information is on our website.
Inclusion: Pending.
Exclusion: Pending.

Denali Therapeutics has plans to prepare for a clinical trial, potentially starting in 2023, with DNL126 in patients with Sanfilippo type A.

DNL126 is an enzyme replacement therapy (ERT) that has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain and can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo more effectively.

Current and planned clinical trials for Sanfilippo Type B

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. Participants 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 phase I/II trial involves an enzyme replacement therapy for Sanfilippo type B called Tralesinidase Alfa, administered weekly into the CSF via a port. Trial locations include Columbia, Germany, Spain, Taiwan, Turkey, the USA, and the UK.

22 Sanfilippo patients have been treated to date. Heparan sulfate levels decreased, and stabilisation or improvement of cognitive development has been seen in younger children. Side effects were related to the delivery site of the therapy.

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 licensing deal was made with a newly-formed biotechnology company, Allievex Corporation, and the therapy was renamed “Tralesinidase Alfa” (AX 250).
This ERT is administered directly into the cerebrospinal fluid of the brain (ICV) via a port implanted under the scalp. The treatment has been well tolerated with no serious adverse events. Data released to date indicates that heparan sulfate in the CSF 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 2-3 years compared to that seen in untreated children with Sanfilippo type B. Of the rapidly-progressing individuals, 40% 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 individuals.

As of February 2021, Allievex reported that 22 individuals with either rapidly or slowly progressing Sanfilippo type B have been treated bi-weekly with Tralesinidase to date. The full clinical trial results have not yet been released but Allievex has indicated that it is making preparations to seek FDA approval for the treatment.

More information about the [trial](#).

---

**Orchard Therapeutics**

TBD | Planning | A | B | C | D

Plans for a Gene Therapy clinical trial, using the patient’s stem cells that are treated and transplanted back into the patient

*Inclusion: Pending.*

*Exclusion: Pending.*

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 a start date is available as yet. More information on the type A trial can be found above, and in the clinicaltrials.gov [summary](#).

---

**JCR Pharmaceuticals**

TBD | Planning | A | B | C | D

Plans for a clinical trial of intravenously-administered Enzyme Replacement Therapy

*Inclusion: Pending.*

*Exclusion: Pending.*

Japanese company, JCR Pharmaceuticals, has plans to prepare for a clinical trial with JR-446 in patients with Sanfilippo type B.

JR-446 is an enzyme replacement therapy (ERT) that has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain and can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo more effectively.

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. An ERT for Sanfilippo type A, JR-441, is also in development. More information is on our website.

**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, which is also in development for Sanfilippo type A, has been engineered to cross the blood-brain barrier to deliver the enzyme to the brain and can be delivered intravenously, potentially treating the neurological symptoms of Sanfilippo more effectively.

**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 gene faulty in Sanfilippo type C - *Hgsnat*. A clinical trial is being planned, but more pre-clinical tests are necessary and the start date is unknown.
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 that is 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 is said to show 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. If results are positive, funding and approval for a clinical trial will be sought.

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 information [here](#).
- Drugs that increase a process called “autophagy” that clears unnecessary or dysfunctional components from cells, allowing them to function better.
  - An example of this is Trehalose, a small sugar. A trial has been planned by [Seelos Therapeutics](#) and Team Sanfilippo Foundation in the USA and Europe. There have been no recent updates on when this trial is expected to start, but discussions were being held with the FDA and EMA regarding trial design.
- 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

**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:** 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 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.

There were 6 children who received treatment in the trial, aged 15-65 months at the time of 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**: 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 2013-2019 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 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.

**Intrathecal injection**
An intrathecal 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 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. Orchard Therapeutics has stem cell therapy for MPS IIIA in clinical trial 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 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.