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Rare Disease

Plain Language Summary of Publication

Gene therapy for children with X-linked myotubular myopathy: a plain language summary of publication for the ASPIRO study

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Summary

What is this summary about?

This summary describes the results of a research study (clinical trial) called ASPIRO that was published in the *Lancet Neurology* in 2023. This study looked at an investigational gene therapy called **resamirigene bilparvovec** (also known as AT132) as a possible treatment for children with a disease called X-linked **myotubular myopathy** (abbreviated as XLMTM).

How to say

- **Myotubular myopathy:** mai-o-tyoo-byuh-luh-r-mai-o-puh-thee
- **Resamirigene bilparvovec:** res-a-mir-i-jeen bil-par-voe-vek
- **Myotubularin:** mai-o-tyoo-byuh-lah-rin

Keywords: gene therapy, **resamirigene bilparvovec**, X-linked **myotubular myopathy**

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Why was the ASPIRO study done?

XLMTM is a rare disease that affects muscles. It is caused by a mutation in a gene called *MTM1*. There are no medicines currently available that can treat the underlying cause of XLMTM in children; treatment of people living with XLMTM is mainly supportive, which means that medication and therapy is focused on reducing the symptoms of the disease. Nearly half of all male children with XLMTM die of respiratory failure or related complications in their first 18 months of life. The ASPIRO study was the first investigational study of a treatment that could potentially treat XLMTM in male children. **Resamirigene bilparvovec** is a gene therapy which is designed to deliver a working copy of the *MTM1* gene to the muscle cells of a person with XLMTM.

Researchers wanted to learn whether **resamirigene bilparvovec** could reduce the need for equipment to support breathing (known as "mechanical ventilation" or "ventilator support") and improve the ability to move in children with XLMTM.

Where can I find the original article on which this summary is based?

The original scientific article on which this summary is based was published in the *Lancet Neurology* and can be accessed at:
https://www.thelancet.com/article/S1474-4422(23)00313-7/fulltext.

The details of the original article are as follows: Shieh PB, Kuntz NL, Dowling JJ, Müller-Felber W, Bönnemann CG, Seferian AM, Servais L, Smith BK, Muntoni F, Blaschek A, Foley AR, Saade DN, Neuhaus S, Alfano LN, Beggs AH, Buj-Bello A, Childers MK, Duong T, Graham RJ, Jain M, Coats J, MacBean V, James ES, Lee J, Mavilio F, Miller W, Varfaj F, Murtagh M, Han C, Noursalehi M, Lawlor MW, Prasad S, Rico S. Safety and efficacy of gene replacement therapy for X-linked myotubular myopathy (ASPIRO): a multinational, open-label, dose-escalation trial. *Lancet Neurol.* 2023;22(12):1125–1139. doi: 10.1016/S1474-4422(23)00313-7.

What were the main results of the study and what do they mean?

Most children with XLMTM who received gene therapy with **resamirigene bilparvovec** had improvements in their ability to breathe without a ventilator, and many gained the ability to sit up, stand, and walk. Some children were even able to walk on their own. Such improvements did not happen in a control group of children with XLMTM who did not receive gene replacement therapy. However, four children who received **resamirigene bilparvovec** died from severe liver disease and investigational research with **resamirigene bilparvovec** was paused (put on clinical hold) due to safety concerns. There is a need to better understand the risk of liver disease in children with XLMTM because their deaths were directly related to a liver response following dosing.

What is XLMTM?

- XLMTM is a rare, genetic muscle disease, mostly present from birth, which is caused by a mutation in the DNA sequence of a gene called *MTM1*.
- The *MTM1* gene provides instructions for creating a protein called **myotubularin**, which is essential for the healthy growth, development, and function of muscle cells.
- XLMTM primarily affects boys because the *MTM1* gene is found on the X chromosome. Genetic females have two copies of the X chromosome, so they usually have one non-mutated copy of *MTM1* which can help prevent symptoms of XLMTM. In ultra rare cases, females may also have inactivation of the non-mutated copy of *MTM1*, causing them to have symptoms. Genetic males only have one copy of the X chromosome and one copy of the Y chromosome.
- Children with XLMTM produce low or no levels of the **myotubularin** protein due to the mutation in the *MTM1* gene. This leads to severe muscle weakness.
- Around half of boys born with the disease die before they are 18 months old. Children with XLMTM are often unable to breathe for themselves and are reliant on equipment to support breathing, known as "mechanical ventilation" or "ventilator support".
- Mechanical ventilation can be either invasive ventilation via a tube into the windpipe (i.e., tracheostomy), or non-invasive ventilation via a mouth piece or mask.
- Most of these children are unable to sit without support, and reaching motor milestones like crawling or walking usually do not happen at all, may only happen briefly, or may be delayed.
- There are no medicines currently available for the treatment of the underlying cause of XLMTM. Management is mainly supportive, which means that healthcare workers give medications and therapies to try to reduce the symptoms of the disease.

Glossary of terms

- **X-linked myotubular myopathy:** a rare muscle disease caused by a mutation in a gene called *MTM1*.
- **Gene:** a section of DNA (i.e., hereditary information) which contains a set of instructions for making a particular protein.
- **Mutation:** a change in the DNA that could potentially affect how the body works.
- **Protein:** a type of molecule that the body uses to grow, stay strong, and do important jobs. All living things are made up of many different proteins with different jobs.
- **Myotubularin:** a protein that is essential for the healthy growth, development, and function of muscle cells.
- **Ventilator support:** equipment that is used to help support breathing in patients who are unable to breathe for themselves.

What is the gene therapy used in the study?

- **Resamirigene bilparvovec** (also known as AT132) is a gene therapy which is designed to deliver the copies of the *MTM1* gene with the correct sequence to the muscle cells of a child with XLMTM in a one-time treatment with lasting effects.
- **Resamirigene bilparvovec** was previously shown to be effective in restoring typical muscular function in animals with XLMTM without any notable adverse reactions; ASPIRO was the first study of this investigational gene therapy performed in humans.
- Children received the gene therapy directly into the veins, via a single intravenous infusion.

Glossary of terms

- **Gene therapy:** a medical treatment that works by transferring correctly-working versions of faulty or missing genes to targeted areas of the body. The aim of gene therapy is to help treat or prevent diseases that are caused by those faulty genes.
- **Resamirigene bilparvovec:** a gene therapy designed to deliver a working copy of the *MTM1* gene to the muscle cells of a person with XLMTM.

Who took part in the study?

The ASPIRO study included 26 children with XLMTM from Canada, France, Germany, and the USA. Many of the children in ASPIRO had been in a previous study, called INCEPTUS (Link), that looked at breathing, motor muscle strength, and health issues due to XLMTM.

The treatment groups were as follows:

- 7 children received the lower dose.
- 17 children received the higher dose.
- 14 children were in the untreated control group.

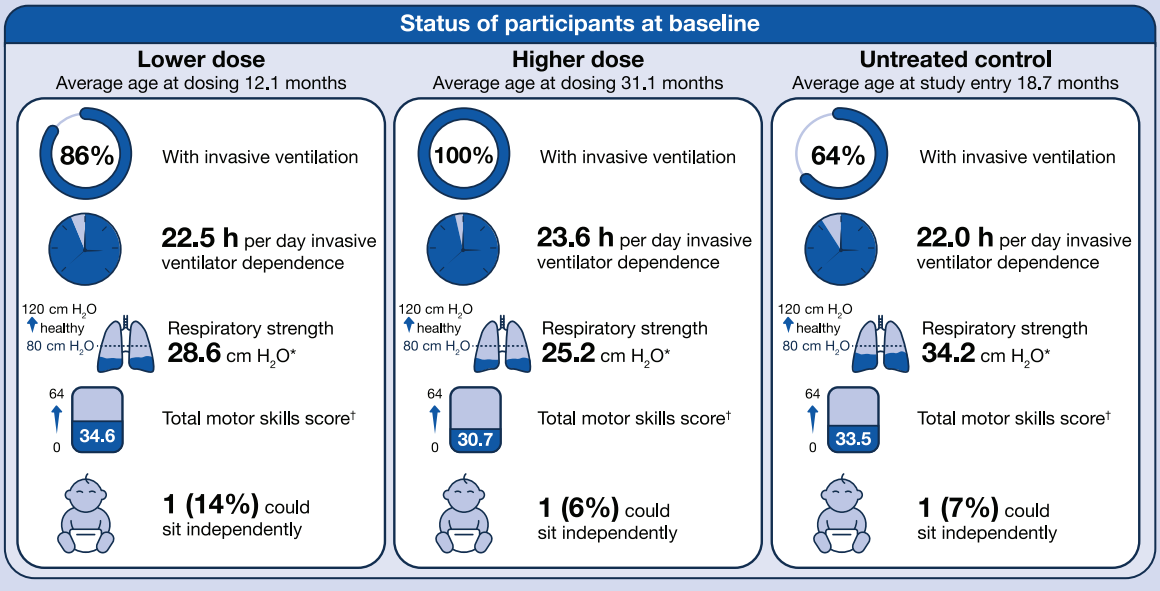
The untreated control group was made up of two children enrolled into ASPIRO who received no treatment and 12 children from the INCEPTUS study who did not receive gene therapy.

Children who took part in the study:

- Were all boys younger than 5 years old or had participated in the previous INCEPTUS study.
- Had a diagnosis of XLMTM that had been confirmed by a genetic test.
- Required mechanical ventilation (either invasive, via a tracheostomy, or non-invasive, via a mask or mouthpiece) to help them breathe.

Glossary of terms

- **Treatment (group):** a group of patients with a specific disease who receive dosing with a treatment, in this case the gene therapy **resamirigene bilparvovec**, being tested in a clinical trial. The treatment group is compared against the control group to see if the treatment is working.
- **Control (group):** a group of patients with a specific disease who do not receive dosing with a treatment, in this case the gene therapy **resamirigene bilparvovec**, being tested in a clinical trial.
- **Motor milestones:** a set of movements that babies and young children will normally develop as they grow. Doctors will check these milestones at specific ages to see if a child is developing normally.



*Respiratory strength is measured as the greatest pressure that the muscles responsible for breathing in can create (called maximal inspiratory pressure or MIP). The lower end of the normal range for children aged 0–4 years is 80 cm H_2O. †Motor skills are assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (abbreviated as CHOP INTEND), out of a maximum score of 64 points.

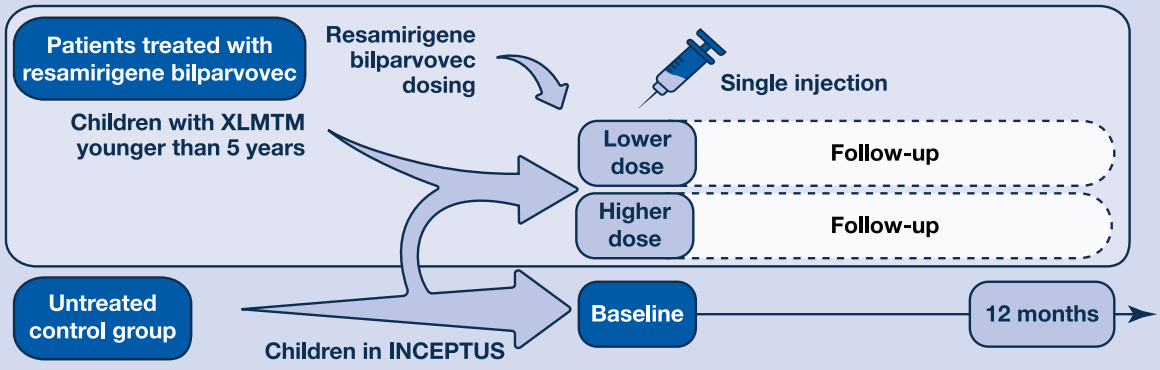
What happened in the study?

ASPIRO was originally designed with two parts:

- Part 1 assessed the safety and increasing doses (dose escalation) of **resamirigene bilparvovec** to identify the best dose for use in further studies
- Part 2 was to use the dose of **resamirigene bilparvovec** selected in part 1 for further study

The study assessed **resamirigene bilparvovec** given as a single injection directly into the children's veins, at one of two dose levels:

- Lower dose (1.3×10^{14} copies of the gene therapy per kilogram of bodyweight)
- Higher dose (3.5×10^{14} copies of the gene therapy per kilogram of bodyweight)



The gene therapy was successfully delivered and laboratory tests of muscle samples showed increases in levels of **myotubularin** protein in the skeletal muscle. During the course of the trial, three children who received the higher dose died. After a safety review, regulatory authorities allowed the trial to continue with dosing at the lower dose only, which meant that the study no longer consisted of two parts. Another death of a child who received the lower dose resulted in regulatory authorities pausing the study (called a clinical hold). Investigational research with **resamirigene bilparvovec** in humans is still on clinical hold. If **resamirigene bilparvovec** was to be used for research in humans at any time in the future, this would be carried out in a new clinical trial that would need to be reviewed by the FDA and other health authorities outside of the USA.

The main question that the researchers wanted to answer in the study was:

Did treatment with **resamirigene bilparvovec** reduce the hours of ventilator support required each day, from the start of the study to week 24 and week 48, compared with the untreated control?

Other questions that the researchers wanted to answer were:

Did treatment with **resamirigene bilparvovec** increase respiratory muscle strength, measured by maximal pressure on breathing in (called maximal inspiratory pressure or MIP), compared with the untreated control group?

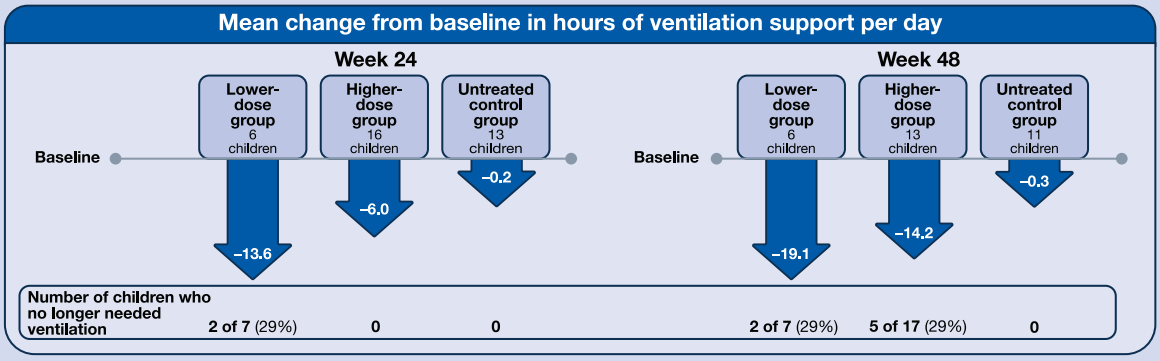
Did treatment with **resamirigene bilparvovec** increase motor skills, measured by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (abbreviated as CHOP INTEND), compared with the untreated control group?

Was treatment with **resamirigene bilparvovec** safe? Did it lead to any unwanted side effects during the study?

What were the main findings of the study

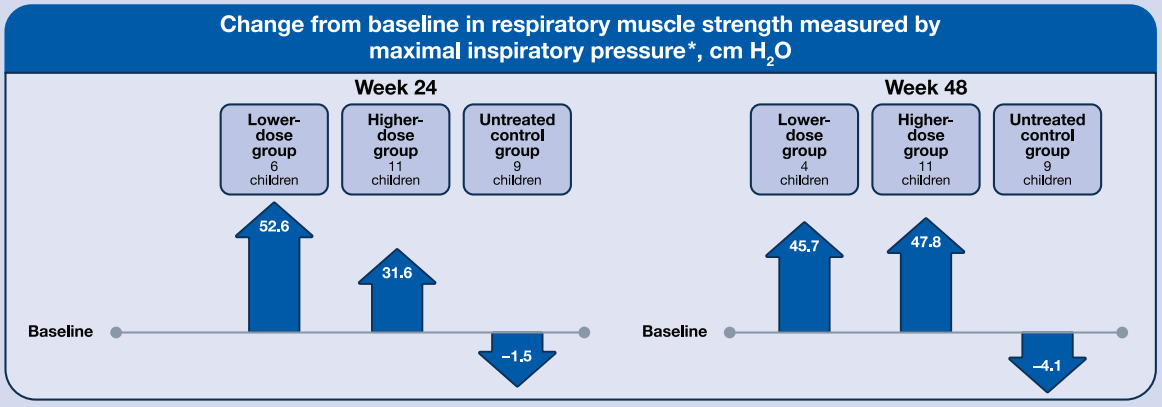
Did treatment with resamirigene bilparvovec reduce the hours of daily mechanical ventilation required relative to the start of the study at week 24 and week 48 following treatment, compared with the untreated control?

- Yes. At 24 and 48 weeks after treatment, improvements were observed in daily hours of ventilation support among children who received either the lower dose or higher dose of **resamirigene bilparvovec** compared with children who received no treatment.
- At 48 weeks after treatment, 29% of children who received the lower dose and 29% of children who received the higher dose no longer needed ventilator support; all children in the untreated control group still required mechanical ventilation support.



Did treatment with resamirigene bilparvovec increase respiratory muscle strength, measured by MIP, compared with the untreated control?

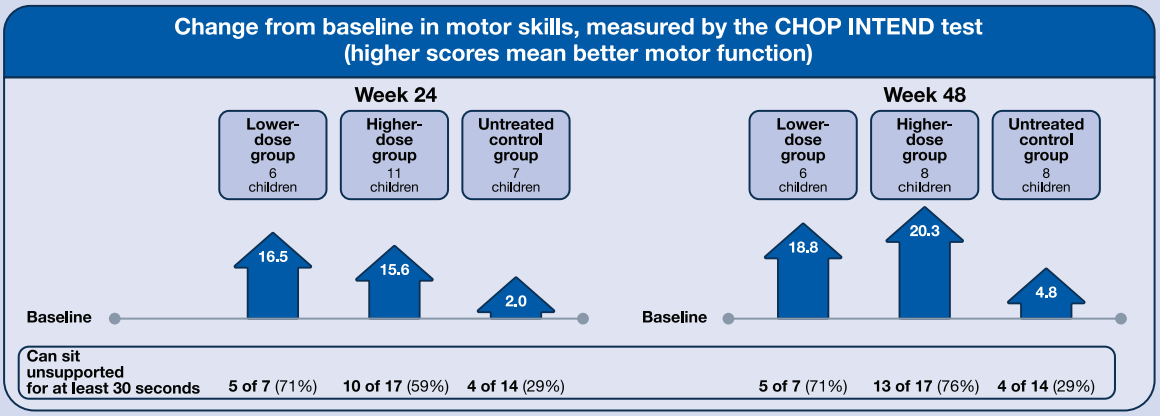
- Yes. Improvements were observed at 24 and 48 weeks after treatment in respiratory muscle strength among children who received either the lower dose or higher dose of **resamirigene bilparvovec** compared with children who received no treatment.



*Respiratory strength is measured as the greatest pressure that the muscles responsible for breathing in can create (called maximal inspiratory pressure or MIP). Higher scores mean greater muscle strength.

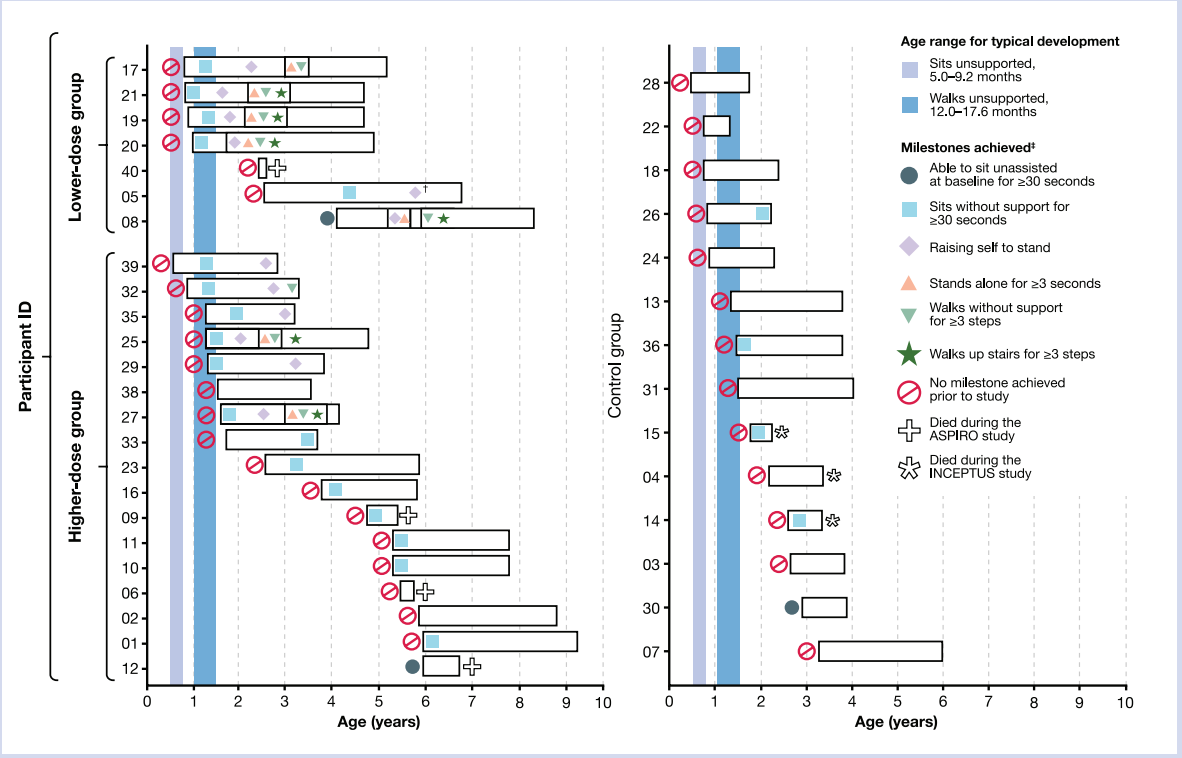
Did treatment with resamirigene bilparvovec increase motor skills, measured by CHOP INTEND, and achievement of motor milestones such as sitting unsupported (measured by the Bayley Scales of Infant Development), compared with the untreated control?

- Yes. At 24 and 48 weeks after treatment, improvements were observed in motor skills in children who received either the lower dose or higher dose of **resamirigene bilparvovec** compared with children who received no treatment.
- At 48 weeks after treatment, 71% of children who received the lower dose and 76% of children who received the higher dose could sit unsupported for at least 30 seconds, compared with 29% of children in the untreated control group.



Motor skills are assessed by the CHOP INTEND, out of a maximum score of 64 points. Ability to sit unsupported for 30 seconds was measured by the Bayley Scales of Infant Development (also known as "Bayley-III assessments").

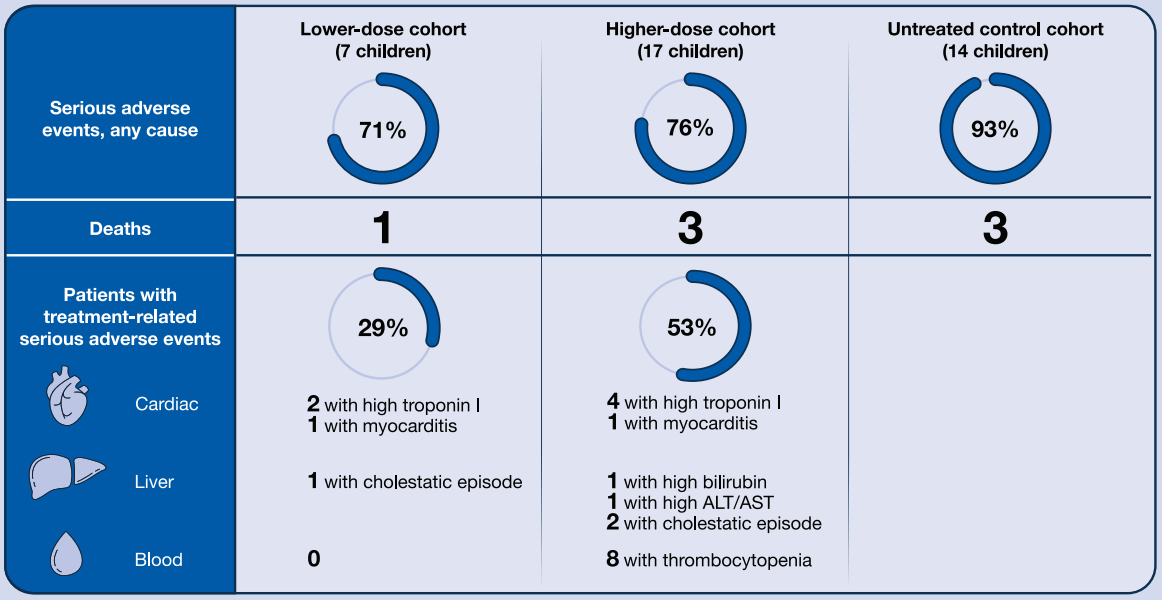
- Over the course of the study (represented by the white boxes), many of the children who received treatment were able to achieve multiple motor milestones, such as sitting without help or walking without support.
- Six (86%) lower-dose participants and 14 (82%) higher-dose participants attained the ability to sit independently for at least 30 seconds (represented by ■) compared with five (36%) control participants.
- Six (86%) lower-dose participants and six (35%) higher-dose participants could pull themselves to stand (represented by ◆) compared with zero control participants.
- Five (71%) lower-dose participants and three (18%) higher-dose participants could walk unsupported (represented by ▼) post dosing compared with zero control participants.



†Participant 05 reached the milestones of sitting independently and raising self to stand, but was not able to do either of these milestones at later assessments.
‡Milestones are based on standard measures of childhood development, known as Bayley Scales of Infant Development or "Bayley-III assessments"

Did treatment with resamirigene bilparvovec lead to side effects during the study?

- Yes. In the lower-dose group, 24 serious side effects were reported among five (71%) of seven children. In the higher-dose group, 58 serious side effects occurred among 13 (76%) of 17 children. These were not necessarily related to the study treatment: similar serious events occurred in 13 (93%) of 14 children in the untreated control group. The serious side effects in treated children that the researchers considered to be treatment-related occurred in two children in the lower-dose group and nine children in the higher-dose group. These mostly involved the heart or liver.
- Three children who received the higher dose of **resamirigene bilparvovec** and one child who received the lower dose of **resamirigene bilparvovec** died from severe liver complications related to cholestasis. These children had intermittent evidence of cholestasis prior to dosing. Cholestasis is a condition that occurs when the flow of bile from the liver is reduced or blocked.
- Three children in the control group died during the study. The causes of these deaths were aspiration pneumonia, chronic bronchopneumonia, and bleeding in the liver, which were not unexpected based on what is known about the course of XLMTM.



A child in the study could experience multiple side effects. The treatment related serious adverse events in heart, liver and blood listed here do not include the patients with treatment related serious adverse events who had died.

Troponin I is a protein that is released into the bloodstream when the heart muscle has been damaged. Myocarditis is inflammation of the heart muscle. ALT (alanine transaminase), AST (aspartate transaminase), and bilirubin are liver enzymes, high levels of which can mean that the liver is injured. Cholestasis is a condition that occurs when the flow of bile from the liver is reduced or blocked. Thrombocytopenia is a condition that occurs when the amount of platelets in the blood, which are needed for clotting, is too low.

What do the findings of the study mean?

The results of the ASPIRO study showed that gene therapy to replace **myotubularin** in muscle cells has the potential to be an effective treatment for this rare, severe, and often fatal disease. Most children with XLMTM who received gene replacement therapy with a single dose of **resamirigene bilparvovec** by injection had significant improvements in their ability to breathe without a ventilator.

- Almost a third of children no longer needed ventilator support by 48 weeks after treatment with either the lower dose or the higher dose of **resamirigene bilparvovec**. This hardly ever happens in children with XLMTM who have not received gene therapy.

Important milestones, such as the ability to sit up, stand, and walk, were achieved by many children with XLMTM who were treated with **resamirigene bilparvovec**, with some even being able to walk on their own. Such improvements are not seen in this population without treatment and were not observed in untreated children with XLMTM in the control group, where three children died from complications due to the disease.

However, four children who received **resamirigene bilparvovec** died from severe liver problems. These deaths revealed that children with XLMTM can develop severe liver complications related to cholestasis, which were different from the liver problems previously known to occur in XLMTM. Research is ongoing to better understand liver disease in children with XLMTM, and how to monitor for potential liver problems before and after any investigational treatment such as gene therapy.

Declarations

Ethics approval and consent to participate

The trial design was reviewed and approved by the institutional review boards of all institutions that took part in the trial. During the design of the study, patient and family meetings were held with the investigators to better understand the human impact of the disease and to help choose the most relevant endpoints to measure in the trial. An independent data and safety monitoring committee monitored the integrity and safety of the trial. Written informed consent to participate was given by the parents or legal guardians of the children in the ASPIRO and INCEPTUS trials.

Author contributions

Perry B. Shieh: Conceptualization; Data curation; Investigation; Writing – review & editing.

Wendy Hughes: Writing – review & editing.

Marie Wood: Writing – review & editing.

Alan H. Beggs: Data curation; Investigation; Writing – review & editing.

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Emma S. James: Project administration; Writing – review & editing.

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Lindsay N. Alfano: Data curation; Investigation; Writing – review & editing.

Tina Duong: Data curation; Investigation; Writing – review & editing.

Mojtaba Noursalehi: Formal analysis; Writing – review & editing.

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Salvador Rico: Conceptualization; Writing – review & editing.

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Competing interests
P.B.S. has received funding and provision of study materials from Astellas Gene Therapies (formerly Audentes Therapeutics) to support clinical trial investigations relating to the present manuscript; has received research grants or contracts from Abcuro, Avidity, Biogen, Dyne, Novartis, Pfizer, PTC Therapeutics, Reveragen, Sarepta, and Solid Biosciences; has received consulting fees for advisory board participation from Alexion, argenx, Biogen, Genentech, Novartis, UCB, Sanofi, and Sarepta; and has received honoraria for lectures or presentations from Alexion, argenx, Biogen, Catalyst, CSL Behring, Genentech, Grifols, and UCB. A.H.B. reports research grants or contracts from the National Institutes of Health, Muscular Dystrophy Association (USA), Astellas Gene Therapies, Chan Zuckerberg Initiative, and A Foundation Building Strength for Nemaline Myopathy; has received consulting fees from Astellas Gene Therapies, Kate Therapeutics, and Roche Pharmaceuticals; has received honoraria for lectures or presentations from GLG and Guidepoint Global; has received support for travel and meeting attendance at the Muscular Dystrophy Association and World Muscle Society; is an executive board member at the World Muscle Society; is an inventor on and has received royalties for a patent for adeno-associated virus gene therapy for XLMTM; and holds stocks in Kate Therapeutics and Kinea Bio. M.W.L. has received research funding from Astellas Gene Therapies to his academic institution (Medical College of Wisconsin) and to his company (Diverge Translational Science Laboratory) for work related to the present manuscript; has received research grants or contracts to his academic institution from Solid Biosciences, Kate Therapeutics, Taysha Therapeutics, Ultragenyx, and Prothelia; has received consulting fees from Astellas Gene Therapies, Encoded Therapeutics, Modis Therapeutics, Lacerta Therapeutics, AGADA Biosciences, Dynacure, Affinia, Voyager, BioMarin, Locanabio, and Vertex Pharmaceuticals; has received speaker fees and reimbursement for travel related to sponsored research from Astellas Gene Therapies; has received personal fees for scientific advisory board participation for Astellas Gene Therapies and Solid Biosciences; his institution has received payment from Taysha Therapeutics for his advisory board participation; and he is currently Chief Executive Officer, founder, and owner of Diverge Translational Science Laboratory, which continues to work under contracts from many gene therapy companies including Astellas Gene Therapies, Solid Biosciences, Kate Therapeutics, Prothelia, Ecogenome, Cure Rare Disease, Rocket Pharma, Ultragenyx, Carbon Biosciences, Locanabio, Regenxbio, Vita Therapeutics, Lexeo Therapeutics, Lovelace Biomedical, Prevail Therapeutics, and Satellos. R.J.G. reports limited consulting fees from Astellas Gene Therapies for work on the ASPIRO study design and clinical outcome measures. N.L.K. has received research funding from Astellas Gene Therapies to her institute as a study site for the ASPIRO clinical trial; has received research grants from Argenx, Biohaven, Biogen, Catalyst, Novartis, Sarepta, and Scholar Rock; has received consulting fees for participation in medical advisory boards for Argenx, Astellas, Catalyst, Genentech, Sarepta, and Scholar Rock; has received honoraria for gene therapy lectures for Sarepta; and is on a data safety monitoring board for Sarepta. J.J.D. has received research grants or contracts from Astellas Gene Therapies to his institute as a study site for the ASPIRO clinical trial and for preclinical studies; and has received an honorarium for a sponsored symposium and support for travel to an international meeting to present data from Astellas Gene Therapies. W.M.-F. has received support for study materials and study personnel relating to the present manuscript from Astellas Gene Therapies; consulting fees from Sarepta, PTC Therapeutics, Novartis, Santhera, and Roche; personal compensation from Novartis, Biogen, Santhera, and Italfarma; and institutional funding from Roche, for lectures; and has also served on scientific advisory boards for Deutsche Gesellschaft für

Muskelkranke and Glykogenosis. C.G.B. has received research grants, contracts, or travel support for various invited lectures at academic meetings from Noelia Foundation, Muscular Dystrophy UK, and Cure CMD; holds a patent for *COL6A1* intron 11 pseudoexon skipping technologies unrelated to the present manuscript; has participated (without fees) in advisory boards for Solid Biosciences (IGNITE trial), Rocket Pharma, and Nationwide Children's Hospital; and is Chair of the Scientific Advisory Board of the MDUK Oxford Neuromuscular Centre. A.B.B. has received consulting fees from Audentes Therapeutics and research funding from the Myotubular Trust for preclinical work related to the present manuscript; and holds a patent on systemic gene replacement therapy for treatment of XLMTM. L.S. has received consulting fees and honoraria for lectures from Astellas Gene Therapies; and was coordinating investigator of the European NatHis-CNM study, funded by Dynacure. V.MacB. has received a research grant for a research study and consulting fees from Astellas Gene Therapies paid both directly to her and her institution. A.R.F. has been a member of an independent data monitoring committee for a different clinical trial for *MTM1*-related myopathy and *DNM2*-related myopathy (the trial was terminated early). A.B. has received honoraria for speaking at scientific meetings, serving at scientific advisory boards from Pfizer, Roche, Novartis, and ITF Pharma; and is a member of the European Reference Network (ERN) for Neuromuscular Diseases. L.N.A. has received grants or contracts from Astellas Gene Therapies via her institution to provide training and quality control services supporting the ASPIRO clinical trial program. T.D. has received consulting fees from Astellas Gene Therapies for study training on the CHOP INTEND measurement in ASPIRO; has served as a consultant for Avidity, Biogen, Dyne, Genzyme, Juvena, Roche, Somite, and Trinds; and had received grants or advisory board fees from Biogen, CureSMA, Duchenne UK, PPMD, Sanofi, and Scholar Rock. J.C., F.V., M.N., W.M., and J.L. were formerly employees of Astellas Gene Therapies. S.P. was an employee at Astellas Gene Therapies from February, 2014, to June, 2019, and was the senior physician overseeing the ASPIRO study. S.R. and E.S.J. were formerly employed by Audentes Therapeutics and, following acquisition, by Astellas Gene Therapies; E.S.J. formerly held stock in Audentes Therapeutics. All other authors declare no competing interests.

Availability of data and materials

Details for how researchers may request access to anonymized participant level data, trial-level data, and protocols from Astellas sponsored clinical trials can be found at https://www.clinicaltrials.astellas.com/transparency/.

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