# Treating Pompe Disease

While there is not yet a cure for Pompe disease, there are treatments that extend and improve the lives of people with Pompe. Researchers continue to study different ways to correct the effects of Pompe, while also working towards finding cures. The process of developing a new treatment involves many steps and can take years.

The following information is a basic overview of some of the strategies in use or in development to treat Pompe disease. We wanted to give readers an idea about the incredible work involved in trying to address this complex disease. Resources and references are suggested to aid in beginning to learn more. It is exciting to know that there are many different approaches to dealing with Pompe. There is so much to be hopeful about for the future.

## Existing Treatments

*Enzyme Replacement Therapy*

The current standard of care for treating Pompe disease is enzyme replacement therapy (ERT). It has been studied and advanced since the mid-90s. The first successful trials for ERT were in 1999, and the first treatment was approved in 2006. ERT has been shown to decrease heart size in IOPD, maintain normal heart function, stabilize or even improve how muscles work, and reduce build-up of glycogen in cells. ERT extends the life of people with classic infantile-onset Pompe disease (IOPD) and slows and sometimes improves disease progression in people with late-onset Pompe disease (LOPD).

ERT works by replacing the GAA enzyme that is missing in the body or is there in only a tiny amount. This lab-made GAA enzyme is called recombinant human GAA (rhGAA). It is given intravenously, through the patient's vein, into the bloodstream. ERT is done on a regular schedule for life.

During ERT, some of the rhGAA does not go into the affected body tissues, like skeletal muscle, as it should. Also, the body's immune system may treat the lab-made rhGAA as a threat and create antibodies against it. These problems limit how well ERT works. Other factors in how well ERT works include age when ERT is started, type of muscle that is affected (type 1 versus type 2), the genetic make-up of the person with Pompe, and disease management.

ERT works best for the heart muscle, but less well for correcting skeletal and smooth muscle disease. It does not correct disease in the central nervous system (brain and spinal cord). There is still work being done to determine best practices using ERT. Given the chances of a strong immune response against rhGAA in some patients, it is important that all patients be carefully monitored for their immune response to ERT. Patients may need immune modulation (see next page).

The development of next generation ERT is on-going to enhance how ERT works. Scientists have created new enzymes by making chemical changes, which improve delivery of the lab-made rhGAA to target tissues during ERT. Studies on another treatment that was recently approved, pharmacological chaperone therapy with ERT, show that the chaperone can enhance how ERT works (see below). Other research shows that nutrition and exercise therapy in combination with ERT is of benefit to people with late-onset Pompe disease. There is even promising clinical research on giving ERT to babies with infantile-onset Pompe disease before they are born. Research continues into the uses and ways to make ERT even more effective.

Learn more at IPA/Pompe Connection -

https://worldpompe.org/resources/patient-focused-publications/

- About Enzyme Replacement Therapy

Please also see medical journal references for ERT on page 5. These references are available on the AMDA website or www.pubmed.gov

**Acid Maltase Deficiency Association**
*PO Box 700248*
San Antonio, Tx 78270
www.amda-pompe.org

## Existing Treatments (continued)

*Immune Modulation*

**C**ross-**R**eactive **I**mmunological **M**aterial or CRIM is a measure of GAA enzyme made naturally in the body. Lab tests can determine CRIM status. Patients whose bodies do not make any GAA enzyme are CRIM-negative (all LOPD patients are CRIM-positive). They typically develop a strong, lasting immune response against the lab-made GAA enzyme, rhGAA, used in ERT.

There are drugs that help limit the immune response already in use for other medical treatments. These drugs have been found to help reduce the body's immune response in patients with Pompe disease. The process is called immune modulation. It is best if the drugs are given at the start of ERT, but even after ERT has been started they can be effective.

In addition, a patient's CRIM status should be determined before the first ERT is given where possible. Knowing CRIM status is essential to improve treatment effect by increasing the amount of rhGAA given and/or combining ERT with immune modulation in patients who are CRIM-negative or are having a poor response to treatment. CRIM-positive patients who make a very small amount of GAA enzyme may also have a poor response to ERT.

Recently, a group of researchers created a personalized tool to determine a CRIM-positive patient's risk of developing antibodies against the immune modulation drugs, which will be helpful in making patient care decisions prior to ERT.

For more information, please see medical journal references for immune modulation on page 5. These references are available on the AMDA website or www.pubmed.gov

*Pharmacological Chaperone Therapy*

Pharmacological chaperone therapy (PCT) aims at restoring the activity of native GAA enzyme in cells (this means the GAA that CRIM-positive patients make naturally in small amounts). Broadly defined, a chaperone is a molecule (smallest unit of a chemical compound) able to assist a protein in recovering its correct form.

For the GAA enzyme to work, it must fold correctly into a specific shape. Pharmacological chaperones are small molecules that have the special ability to bind to the non-working GAA enzyme and correct its misfolded shape in some cases. This allows increased enzyme activity in cells.

Research on PCT has indicated there is better ability of the GAA enzyme to be absorbed and used by the body, the possibility of reaching the brain, and that it can be taken by mouth, as compared to ERT. However, research studies of Pompe patients using PCT alone had to be stopped due to adverse events in patients.

Pharmacological chaperones have been shown to enhance how well ERT works. The good news is that PCT, in combination with ERT, can be used safely and effectively for some Pompe patients. In 2023, the U.S. Food and Drug Administration (FDA) approved the use of combined PCT/ERT for treatment of LOPD in adults who meet certain criteria. Patients on this combined treatment have demonstrated improved lung function. Research is on-going.

For more information, please see medical journal references for PCT on page 5. These references are available on the AMDA website or www.pubmed.gov

## Treatments in Development

*Substrate Reduction Therapy*

Without GAA enzyme, glycogen builds up inside of the body's cells and destroys them. This process leads to Pompe disease symptoms. The goal of substrate reduction therapy (SRT) is to slow the build-up of glycogen by blocking its production. It works by stopping or slowing the activity of the enzyme that makes glycogen in muscle cells. The idea is that preventing the toxic build-up of glycogen in muscles will slow down disease progression in patients with late-onset Pompe disease.

SRT may also be combined with ERT to benefit patients across the Pompe disease spectrum. Researchers are currently testing SRT medications that can be taken by mouth, while others are looking at intravenous (IV) applications. Other researchers are working on genetic SRT, which uses the cell's natural machinery to stop the target gene's expression.

For more information, please see medical journal references for SRT on page 6. These references are available on the AMDA website or www.pubmed.gov

*Gene Therapy*

Gene therapy is a promising way to treat IOPD and LOPD that has benefits over ERT. It is longer lasting and provides a consistent amount of GAA enzyme to the body. Some gene therapies can correct disease in skeletal muscle and some may correct glycogen accumulation in the central nervous system (brain and spinal cord). The aim is to increase the ability of target body tissues to make the GAA enzyme, and also to remove the need to have regular infusions of ERT.

There are different approaches to gene therapy. In one approach, a vector, or vehicle, which contains the working GAA gene is delivered directly inside the patient's body (in vivo). This vector, (the most common approach is with AAV), transfers the GAA gene to target tissue cells like the liver. With the GAA gene, cells in the target tissue can make the GAA enzyme. Liver cells are of interest because the human liver has a special ability to create immune tolerance.

*Gene Therapy (continued)*

By putting the working GAA gene into liver cells, the liver can produce GAA enzyme and become an "enzyme factory" for the entire body. The liver then potentially becomes a stable source of GAA enzyme production in the body; it is just not yet known how long this will last.

This approach also avoids the problem of a strong immune response against GAA enzyme. In vivo gene therapy research involves different AAV vectors and routes of delivery into distinct target body tissues to find out what works best for different patients. However, it is unclear at this time how long this form of gene therapy will last, but current knowledge indicates that this approach is most appropriate for those who have reached their full growth potential. The understanding is that as a child grows, their liver increases in size and if given too early, the GAA gene would be "flushed out," and no longer provide an adequate supply of enzyme. There is on-going research on this topic.

Another approach is done outside the patient's body (ex vivo). It involves taking bone marrow stem cells from a patient and then using another kind of vector (generally lentiviral), to transfer the working GAA gene into the bone marrow stem cells. This process is done in the lab. Then, the stem cells are transplanted back into the patient by an IV infusion. The new working gene in the patient's bone marrow stem cells gives instructions to increase the amount of GAA enzyme made to slow or stop symptoms of Pompe disease. Theoretically, this would be a permanent approach, and would last the patient's lifetime.

There is much to learn about the different gene therapy approaches. Research is on-going to make gene therapies for Pompe disease a reality. There are clinical trials that are on-going in this area (see Participating in Research below).

For more information, please see medical journal references for gene therapies on page 6. These references are available on the AMDA website or www.pubmed.gov

You can also learn more about gene therapies from the following resources:

*Gene Therapy Resources*

- IPA/Pompe Connections
  https://worldpompe.org/resources/patient-focused-publications/
  - Guide to Cell and Gene Therapies

- National Organization for Rare Disorders (NORD) – Gene Therapy for Rare Diseases
  https://rarediseases.org/gene-therapy
  (this site also has a fact sheet on gene therapy and access to a Podcast titled "Ungeeking the Speak: Dr. Rachel Bailey Talks "Gene Therapy 101"

- American Society of Gene and Cell Therapy: Gene Therapy and Pompe Disease
  https://patienteducation.asgct.org/disease-treatments/pompe-disease

- https://ClinicalTrials.gov (use keywords Pompe, gene therapy to search)

## Participating in Research

*Clinical Trials*

Clinical trials determine if a new test or treatment for a disease is effective and safe. Every clinical trial has an action plan for carrying out the research study. Each clinical trial has its own rules about participation, called inclusion/exclusion criteria. In the U.S., an independent committee of doctors, researchers, and community members must approve and monitor the action plan. They make sure that the risks are low and potential benefits worth the risks. Clinical trials have four phases. Refer to IPA/Pompe Connection's Medical Progress in Pompe Disease for an explanation of the phases and other information. Once a treatment is available, more studies may be done to look at how well the treatment works and its safety during routine use. Studies may also look at the treatment in different patient groups.

Clinical trials are carried out at major medical research centers such as teaching hospitals, at special clinics, and even in doctors' offices. Studies are often done while the patient is in the hospital. Other studies are done on an outpatient basis (in a clinic, not hospitalized).

*Clinical Trials (continued)*

Although studies vary widely, some things should be expected by participants in almost any clinical trial. For example, tests to check on disease status might be more frequent. Also, study participants are often required to keep detailed records of their symptoms and follow strict schedules. They also may be required to travel frequently to study sites.

For rare disorders like Pompe disease, taking part in a clinical trial may give patients access to experimental treatments that could improve, save, or extend their lives. The NIH National Library of Medicine has a database of clinical studies conducted around the world. People can search for clinical trials, including for Pompe disease, at ClinicialTrials.gov.
Information for families/patients about how to use the database can be found at https://classic.clinicaltrials.gov/ct2/help/for-patient.

We also suggest that you contact the AMDA Patient Advocate, Marsha Zimmerman, RN, at marsha.zimmerman@amda-pompe.org for guidance on clinical trials for Pompe disease.

Learn more at:

AMDA General Information on Clinical Trials
https://amda-pompe.org/general-information-on-clinical trials/

AMDA Webinar – Design and Performance of Clinical Trials
https://www.youtube.com/watch?v=aX8zGhbzHO8&feature=youtu.be

National Organization for Rare Diseases – Explore Clinical Trials:

https://rarediseases.org/living-with-a-rare-disease/clinical-trials/

https://rarediseases.org/rare-diseases/pompe-disease/#investigational-therapies

# References

The following references are available on the AMDA website or https://www.pubmed.gov

## Enzyme Replacement Therapy


- Güngör, D., Kruijshaar, M. E., Plug, I., D'Agostino, R. B., Hagemans, M. L., van Doorn, P. A., ... & van der Ploeg, A. T. (2013). Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study. *Orphanet journal of rare diseases*, *8*(1), 1-7.
- Kishnani, P. S., & Beckemeyer, A. A. (2014). New therapeutic approaches for Pompe disease: enzyme replacement therapy and beyond. *Pediatric endocrinology reviews: PER*, 12, 114-124.
- van der Meijden, C. (2017). Pompe Disease in Children and Adults: Further Insights into the Clinical Presentation and Long-Term Effects of ERT: An example of sustainable data collection in rare diseases. Erasmus University Rotterdam
- Chen, M., Zhang, L., & Quan, S. (2017). Enzyme replacement therapy for infantile-onset Pompe disease. *Cochrane Database of Systematic Reviews*, (11).
- Angelini, C. (2021). Exercise, nutrition and enzyme replacement therapy are efficacious in adult Pompe patients: report from EPOC Consortium. *European Journal of Translational Myology*, *31*(2).
- Cohen, J. L., Chakraborty, P., Fung-Kee-Fung, K., Schwab, M. E., Bali, D., Young, S. P., ... & MacKenzie, T. C. (2022). In utero enzyme-replacement therapy for infantile-onset Pompe's disease. *New England Journal of Medicine*, *387*(23), 2150-2158.


## Immune Modulation


- Richard, E., Douillard-Guilloux, G., & Caillaud, C. (2011). New insights into therapeutic options for Pompe disease. *IUBMB life*, *63*(11), 979-986.
- Banugaria, S. G., Patel, T. T., & Kishnani, P. S. (2012). Immune modulation in Pompe disease treated with enzyme replacement therapy. *Expert Review of Clinical Immunology*, *8*(6), 497-499.
- Kazi, Z. B., Desai, A. K., Berrier, K. L., Troxler, R. B., Wang, R. Y., Abdul-Rahman, O. A., ... & Kishnani, P. S. (2017). Sustained immune tolerance induction in enzyme replacement therapy–treated CRIM-negative patients with infantile Pompe disease. *JCI insight*, *2*(16).
- Bolano-Diaz, C., Diaz-Manera, J. (2022). Therapeutic options for the management of Pompe disease: Current challenges and clinical evidence in therapeutics and clinical risk management. *Therapeutics and Clinical Risk Management*. 18:1099-1115.


## Pharmacological Chaperone Therapy


- Porto, C., Cardone, M., Fontana, F., Rossi, B., Tuzzi, M. R., Tarallo, A., ... & Parenti, G. (2009). The pharmacological chaperone N-butyldeoxynojirimycin enhances enzyme replacement therapy in Pompe disease fibroblasts. *Molecular Therapy*, *17*(6), 964-971.
- Roig-Zamboni, V., Cobucci-Ponzano, B., Iacono, R., Ferrara, M. C., Germany, S., Bourne, Y., ... & Sulzenbacher, G. (2017). Structure of human lysosomal acid α-glucosidase–a guide for the treatment of Pompe disease. *Nature communications*, *8*(1), 1111.
- Borie-Guichot, M., Tran, M. L., Génisson, Y., Ballereau, S., & Dehoux, C. (2021). Pharmacological chaperone therapy for Pompe disease. *Molecules*, *26*(23), 7223.
- https://www.fda.gov/drugs/development-approval-process-drugs/drug-trials-snapshots-pombiliti (accessed 03.29.24)

# References (continued)

The following references are available on the AMDA website or https://www.pubmed.gov

## Substrate Reduction Therapy


- Clayton, N. P., Nelson, C. A., Weeden, T., Taylor, K. M., Moreland, R. J., Scheule, R. K., ... & Wentworth, B. M. (2014). Antisense oligonucleotide-mediated suppression of muscle glycogen synthase 1 synthesis as an approach for substrate reduction therapy of Pompe disease. *Molecular therapy-Nucleic acids*, 3, e206.
- Coutinho, M. F., Santos, J. I., & Alves, S. (2016). Less Is More: Substrate Reduction Therapy for Lysosomal Storage Disorders. *Int J Mol Sci*. Jul 4;17(7):1065.
- Coutinho, M. F., Santos, J. I., Matos, L., & Alves, S. (2016). Genetic substrate reduction therapy: a promising approach for lysosomal storage disorders. *Diseases*, *4*(4), 33.
- Bolano-Diaz, C., Diaz-Manera, J. (2022). Therapeutic options for the management of Pompe disease: Current challenges and clinical evidence in therapeutics and clinical risk management. *Therapeutics and Clinical Risk Management*. 18:1099-1115.


## Gene Therapy


- Bond, J. E., Kishnani, P. S., & Koeberl, D. D. (2019). Immunomodulatory, liver depot gene therapy for Pompe disease. *Cell Immunol*. Aug;342:103737.
- Ronzitti, G., Collaud, F., LaForet, P., & Mingozzi, F. (2019). Progress and challenges of gene therapy for Pompe disease. *Annals of Translational Medicine*, 7(13).
- Salabarria, S. M., Nair, J., Clement, N., Smith, B. K., Raben, N., Fuller, D. D., ... & Corti, M. (2020). Advancements in AAV-mediated gene therapy for Pompe disease. *Journal of Neuromuscular Diseases*, *7*(1), 15-31.
- Unnisa, Z., Yoon, J. K., et al. (2022). Gene therapy developments for Pompe disease. Biomedicines, 10, 302
- Liang, Q., Vlaar, E. C., Catalano, F., Pijnenburg, J. M., Stok, M., van Helsdingen, Y.,…van der PloM.eg, A.T., Pijnappel, W. W.M. Pim, van Til, N. P. (2022). Lentiviral gene therapy prevents anti-human acid α-glucosidase antibody formation in murine Pompe disease. *Molecular Therapy-Methods & Clinical Development*, 25, 520-532.
- Liang, Q., Catalano, F., Vlaar, E. C., Pijnenburg, J. M., Stok, M., van Helsdingen, Y., ... & Pijnappel, W. P. (2022). IGF2-tagging of GAA promotes full correction of murine Pompe disease at a clinically relevant dosage of lentiviral gene therapy. *Molecular Therapy-Methods & Clinical Development*, *27*, 109-130
- Roger, A. L., Sethi, R., Huston, M. L., Scarrow, E., Bao-Dai, J., Lai, E., Biswas, D. D, Hadded, L. E., Strickland, L. M., Kishnani, P. S., & ElMallah, M. K. (2022). What's new and what's next for gene therapy in Pompe disease? Expert Opinion on Biological Therapy, 22:9, 1117-1135.


*Posted on the AMDA website-04/05/24*