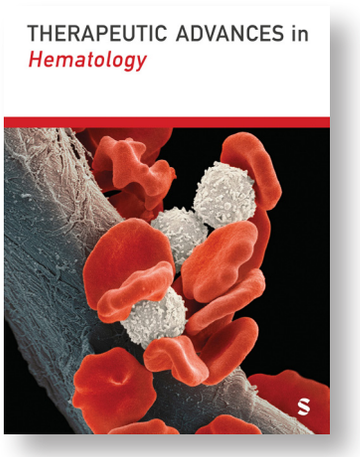
THERAPEUTIC ADVANCES in
Hematology

Plain Language Summary of Publication

Plain language summary: How safe and effective is long-term treatment with intravenous plasminogen concentrate for people with type 1 plasminogen deficiency?



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Summary

What is this study about?

Type 1 plasminogen deficiency (PLGD-1 for short) is a long-term, ultra-rare condition where the body does not make enough of a protein called plasminogen. This can cause thick layers made of a fibrous, insoluble protein called fibrin (known as lesions) to develop in different parts of the body. Intravenous plasminogen concentrate (IV PLG concentrate for short, also known as RYPLAZIM®) is the first medicine approved to treat this condition. It works by replacing plasminogen in the body. In this study, adults and children with PLGD-1 received long-term treatment with IV PLG concentrate. They had already received IV PLG concentrate before, as part of the clinical trial that led to the approval of the treatment, or through the expanded access programs. The researchers wanted to know how safe and effective long-term treatment with IV PLG concentrate was. They also wanted to explore whether giving IV PLG concentrate more or less often would affect how well the treatment worked.

How to say it...

- **Deficiency:** deh-FIH-shun-see
- **Fibrin:** FAI-brin
- **Hypoplasminogenemia:** HI-po-plahs-MIN-oh-jen-ee-me-uh
- **Intravenous:** in-truh-VEE-nuhs
- **Lesion:** LEE-shun
- **Mucous:** MYOO-khus
- **Plasminogen:** plaz-MIH-nuh-jen
- **RYPLAZIM:** RIP-la-zeem

What were the results?

Study participants had no new lesions associated with PLGD-1 or return of previous lesions when they received the treatment as prescribed. Some participants had previous lesions come back when they received the treatment less often than prescribed. These lesions rapidly improved or went away again when they started more frequent treatment, as originally prescribed. Most of the adverse events that participants experienced were classified as mild, and none were related to the study treatment.

What do the results mean?

Overall, long-term treatment with IV PLG concentrate is effective for people living with PLGD-1 and is well tolerated. Treatment with IV PLG concentrate can be personalized to meet people's individual needs.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you understand the findings from recent research.

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

You can read the original article titled 'Safety and efficacy of long-term treatment of type 1 plasminogen deficient patients with intravenous plasminogen replacement therapy' published in the journal *Haemophilia* for free at: https://doi.org/10.1111/hae.70019

Who sponsored the study and this summary?

The study was **sponsored** by Prometic Biotherapeutics Inc., currently Kedrion Biopharma Inc. This summary was sponsored by Kedrion Biopharma Inc.

Who is this summary for?

This summary may be of interest to people living with PLGD-1, their families, and caregivers. Patient advocates, patient organizations, healthcare professionals, and funders of healthcare services may also find this summary useful.

Keywords: plain language summary; lay summary; type 1 plasminogen deficiency.

Study sponsor: a company or organization that oversees and funds a research study. The sponsor also collects and analyzes the information that was generated during the study. In this case, the study treatment is manufactured by Prometic Bioproduction Inc. This company is now doing business as Kedrion Biopharma Canada. It is an **affiliate** of Kedrion Biopharma Inc. and a **subsidiary** of Kedrion S.p.A.

Affiliate: when the parent company owns less than 50% of another company this is known as an affiliate company.

Subsidiary: when the parent company holds a majority ownership of over 50% of another company this is known as a subsidiary.

What is PLGD-1?

Type 1 plasminogen deficiency (PLGD-1 for short) is an **ultra-rare inherited condition**. It is caused by a **gene** change that is passed down in families, from biological parents to children. This gene is called *PLG* and provides instructions for making a protein called **plasminogen**. To develop PLGD-1, children need to inherit 2 copies of a gene change, which means that each biological parent must carry the altered gene (1 copy is inherited from each parent).

- It affects 1 to 2 in a million people. This could mean that around 500 people in the US are affected.

Type 1 plasminogen deficiency (PLGD-1 for short): an ultra-rare inherited condition where the body does not make enough plasminogen. This can lead to abnormal membranes made of fibrin (called lesions) developing in different parts of the body, which can interfere with different bodily functions. PLGD-1 affects 1 to 2 in a million people worldwide; this could mean that around 500 people in the US are affected. It is also called hypoplasminogenemia.

Ultra-rare condition: a condition affecting fewer than 1 in 50,000 people in a given population.

Inherited condition: a health condition caused by a change or error (also called a mutation) in one or more genes, that is passed down in families from biological parents to children.

Gene: a section of deoxyribonucleic acid (DNA for short) that carries instructions for how the body develops and functions. DNA is the genetic material inside cells that is passed from parents to their biological children. Changes in genes (also known as gene mutations) can lead to inherited conditions.

Plasminogen: a protein made in the liver and other organs that circulates around the body in the blood. It plays an important role in breaking down fibrin.

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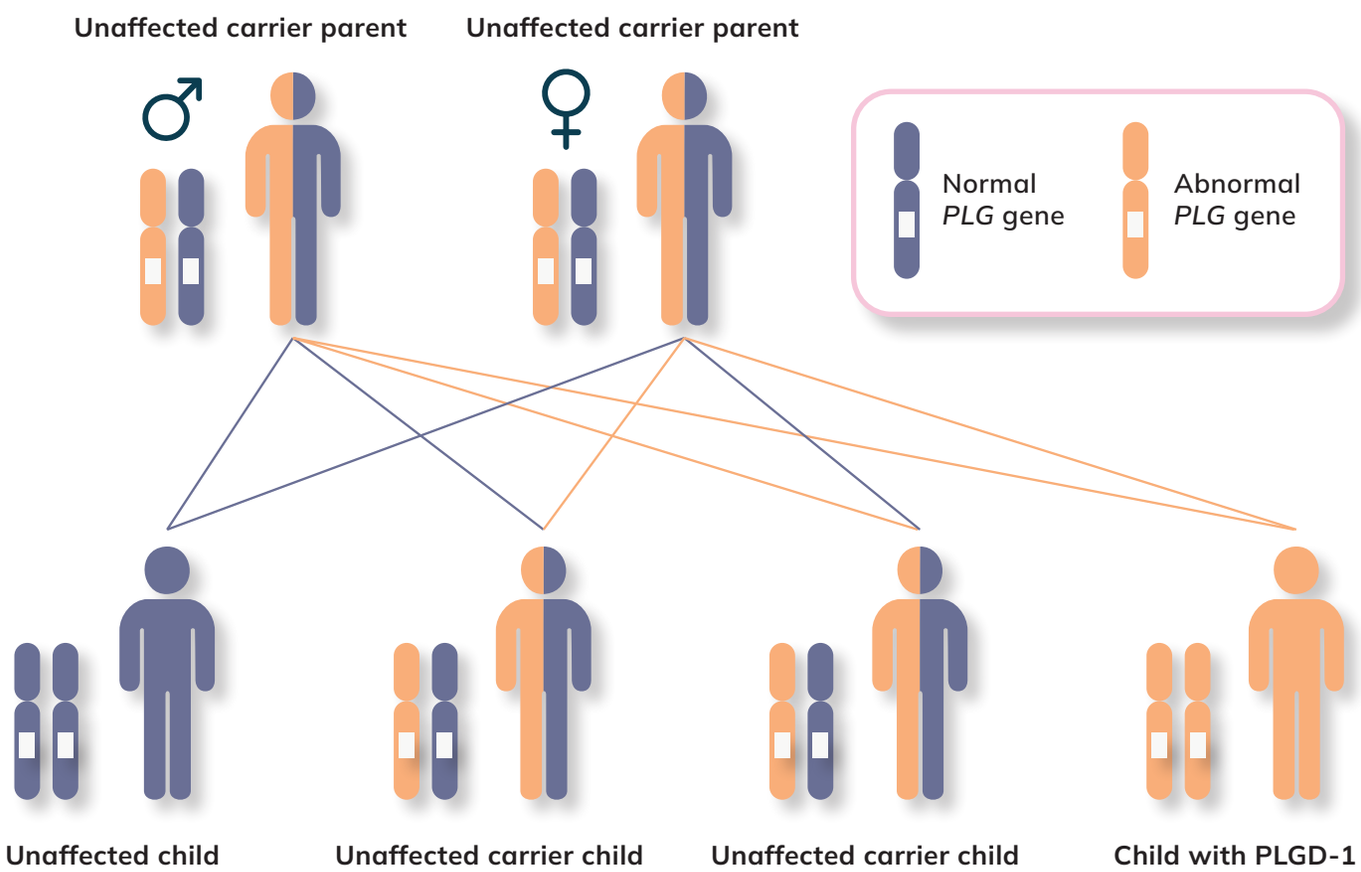
Genetic inheritance diagram showing parental carrier status and possible child outcomes



For a child to have PLGD-1, both parents must be carriers of the abnormal *PLG* gene. The child with PLGD-1 must inherit 1 copy of the abnormal gene from each parent.

Plasminogen is a protein made in the liver and other organs. It circulates around the body in the blood. When doctors measure how well plasminogen is working, they use a percentage scale where normal activity is between 70% and 130%. This means that in people without PLGD-1, plasminogen is typically working at a level within this range.

Plasminogen helps break down another protein called **fibrin** which helps form blood clots and is important for healing wounds. In people without PLGD-1, the activated form of plasminogen (known as **plasmin**) breaks down fibrin during wound healing. This allows new healthy tissue to grow.

People living with PLGD-1 have less plasminogen in their blood than usual. This causes fibrin to build up. It can lead to abnormal layers made of fibrin (called lesions) developing in different parts of the body, especially areas affected by injury, infection, or surgery. These lesions most often occur on the mucous membranes. These are the soft, moist linings of parts of the body that are open to the outside world, such as inside the eyelids and mouth. Other affected areas can include the inside of the ears, nose, airways, vagina, womb, kidneys, and brain, as well as the stomach and intestines.

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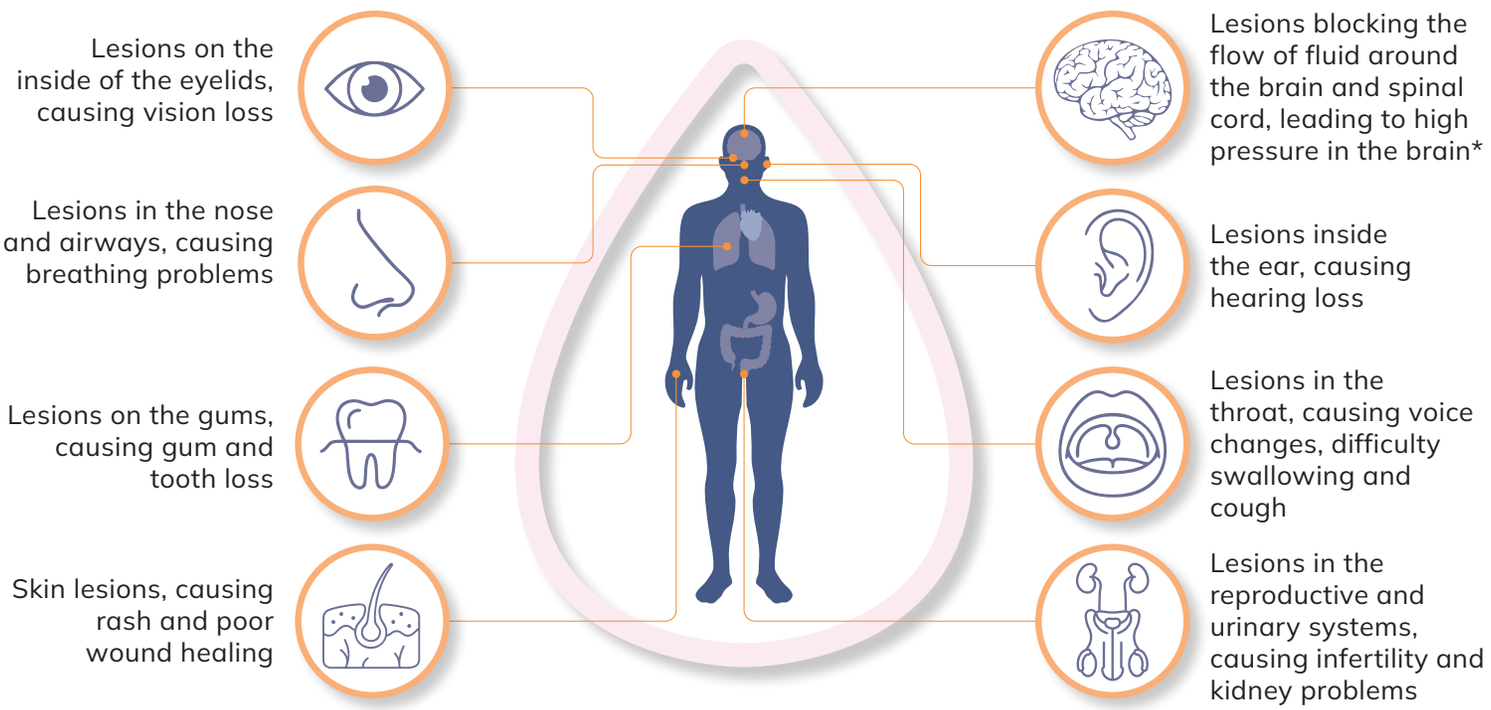
Fibrin: a protein that forms a sticky network of fibers at the site of an injury. This forms the framework for blood clots, which act like glue to stop bleeding from the injury. It also plays an important role in healing wounds.

Plasmin: a protein that is the activated form of plasminogen.

Without treatment, these lesions can cause symptoms that can severely affect people's quality of life and can be life-threatening.

Excessive blood clotting (thrombosis) is not a symptom of PLGD-1.

Where lesions can affect the body



*This problem can be present in babies at birth and can be very serious if left untreated

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What treatments do people living with PLGD-1 receive?

Removal of specific lesions in people living with PLGD-1 does not address the underlying causes of the condition, so it is often not a long-term solution. Surgery to remove the lesions may be helpful for a short period of time under certain circumstances. However, the lesions often come back quickly without treatment to replace the missing plasminogen.

Fresh frozen plasma (FFP for short) from healthy donors has been used to replace the missing plasminogen in a person's blood. However, the amount of plasminogen in FFP is low, therefore, people require numerous treatment infusions.

- Receiving fluid as part of the infusions can lead to too much fluid building up in the body. This can overload the heart and cause fluid to build up in the lungs.
- People can also have unwanted reactions to other proteins in the FFP.

The first specific treatment for people living with PLGD-1 is called **intravenous plasminogen concentrate (IV PLG concentrate for short)**.

Plasma: a straw-colored liquid that forms part of the blood. It carries different blood cells and substances such as proteins around the body.

Fresh frozen plasma (FFP for short): the liquid part of blood, which is collected from donors and frozen shortly after donation.

Intravenous plasminogen concentrate (IV PLG concentrate for short, RYPLAZIM®): a medicine that is a concentrate of plasminogen made from the donated plasma of healthy people, and given to patients as an infusion into the vein.

What is IV PLG concentrate?

In 2021, the **US Food and Drug Administration (FDA for short)** approved IV PLG concentrate as a treatment for people living with PLGD-1. IV PLG concentrate is also known as RYPLAZIM®, or plasminogen, human-tvmh. Approval varies by country; please check with your local healthcare provider for more details.

IV PLG concentrate is a concentrated form of plasminogen made from plasma donated by healthy people. It is given as an injection through a needle into a vein.

The FDA approval was based on information from a **clinical trial** looking at how safe and effective the medicine was for people living with PLGD-1. This study included 6 children and 9 adults who received up to 124 weeks (around 2.5 years) of treatment with IV PLG concentrate. You can find more information on this study here:

- https://clinicaltrials.gov/study/NCT02690714

Treatment with IV PLG concentrate temporarily increases the levels of plasminogen in the blood. By replacing the missing plasminogen, IV PLG concentrate works to decrease or clear lesions.

IV PLG concentrate is the main treatment for PLGD-1 in regions where it is approved.

US Food and Drug Administration (FDA for short): the US government agency responsible for protecting public health by regulating, approving, and ensuring the safety of food and drug products and treatments.

Clinical trial: a research study that determines the safety and effectiveness of a treatment for people with a specific health condition.

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What was the aim of the study?

This study looked at long-term treatment with IV PLG concentrate for people living with PLGD-1. The researchers wanted to know how safe and effective long-term treatment was. They also looked at whether giving IV PLG concentrate more or less often would affect how well the treatment worked.

What type of study is this?

This is a long-term study.

Who took part in the study?

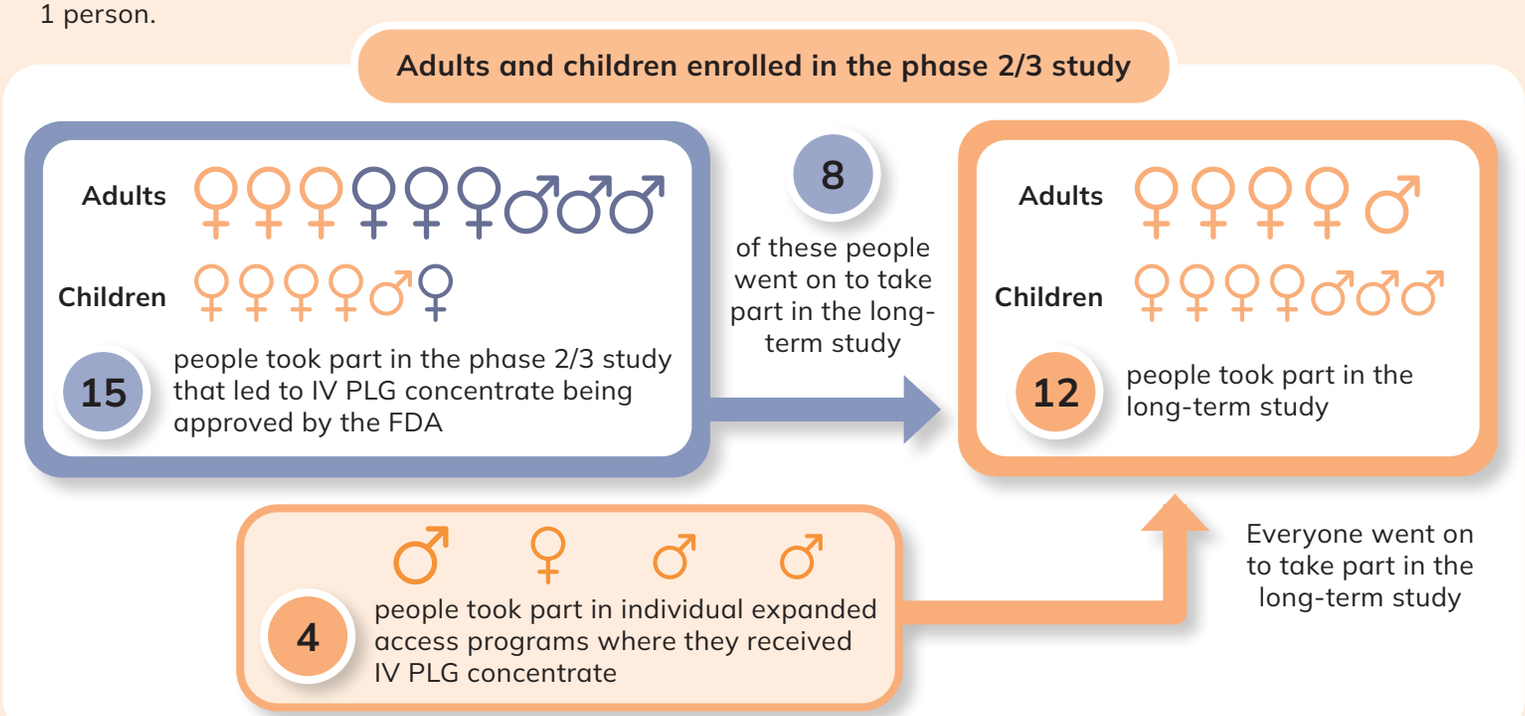
12 people living with PLGD-1 took part in this study

5 adults (aged 18 years and older) and 7 children (aged under 18 years) living with PLGD-1 took part in this study. They received treatment at 3 centers in the US: California, Indiana, and Tennessee. Their age at 1st dose in the phase 2/3 study or expanded access programs ranged between 16 months and 39 years; 8 participants were female and 4 participants were male.

Expanded access program: also known as a compassionate use program. This is a pathway that allows people with serious or life-threatening conditions, who have no other suitable treatment options, to access treatments that are not yet approved in the country where they live for use outside of clinical trials.

These participants had already taken part in either:

- The study that led to the approval of IV PLG concentrate by the FDA.
- An individual expanded access trial. These are a type of **expanded access program**, which is set up for people to receive experimental medicines outside of clinical trials. Individual expanded access trials provide treatment to 1 or more people based on their particular circumstances. In this study, each individual expanded access trial included 1 person.



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Everyone experienced improvement in their lesions during the studies that they took part in before entering this long-term study. 2 children had no lesions before entering their previous study. 10 adults and children had lesions in body areas including the eyes, gums, reproductive system, kidneys, airways, brain, and intestines. 2 participants had life-threatening lesions in their airways which stopped them being able to breathe normally.

Everyone received IV PLG concentrate as an infusion into a vein, at a dose of 6.6 milligrams per kilogram of body weight. Each infusion of IV PLG concentrate took between 10 and 30 minutes. Infusions were given at home, or when participants were admitted to hospital or visited their study center.

- In the long-term study, everyone received IV PLG concentrate every 3 to 7 days at first. The study doctors then adjusted how often participants received treatment, based on:
  - Their level of active plasminogen. This was measured using blood tests.
  - How their lesions responded to treatment.
  - Whether IV PLG concentrate was available. There were 2 periods where the supply of IV PLG concentrate was limited, delaying the time to next treatment.

How often people received treatment in the long-term study was decided by study doctors according to their professional judgement, rather than following a study rule book, also known as a protocol.

What was measured?

In this study, researchers looked at:

- Changes in participants' lesions, and whether any new lesions appeared;
- Any **adverse events** that participants experienced; and
- How often participants received treatment.

Adverse event: an unintended event that happens when taking a medicine and may negatively impact health and wellbeing. Adverse events may or may not be directly caused by the medicine itself. Some adverse events are classified as mild, while others can be more serious. An adverse event is considered 'serious' if it results in death, is life-threatening, requires hospitalization, or leads to significant long-term disability.

What were the results of the study?

The length of time that participants received IV PLG concentrate treatment ranged between 25 and 42 months (approximately between 2 and 3 and a half years).

*approximately 3 and a half years

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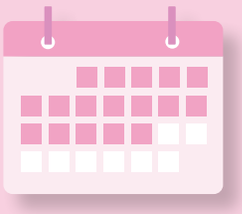
The length of time that participants received IV PLG concentrate treatment ranged between 28 and 71 months (approximately between 2 and 6 years).

When the researchers included the IV PLG concentrate treatment that participants received in their previous study before entering this study, people received treatment for



68 months* on average

*approximately 5 and a half years

On average, people received

172 infusions of IV PLG concentrate during the study

This was equivalent to around 5 infusions per month.

Some participants had lesions that came back when they received less frequent treatments

Once their condition was controlled, many participants stayed free from new lesions with a personalized treatment regimen. There were 2 periods where there were problems with the supply of IV PLG concentrate and participants received less frequent treatment. During this time:

Lesion recurrence outcomes

♀♂♀♀♀	**Adults**	♀♂♀♀♀
♀♀♀♀♂♂♂	**Children**	♀♀♀♀♂♂♂
One-third of people (**4** out of **12**) had lesions that came back. These lesions rapidly improved or went away once the frequency of the treatments was increased		Two-thirds of people (**8** out of **12**) did not have lesions that came back, despite having less frequent treatments

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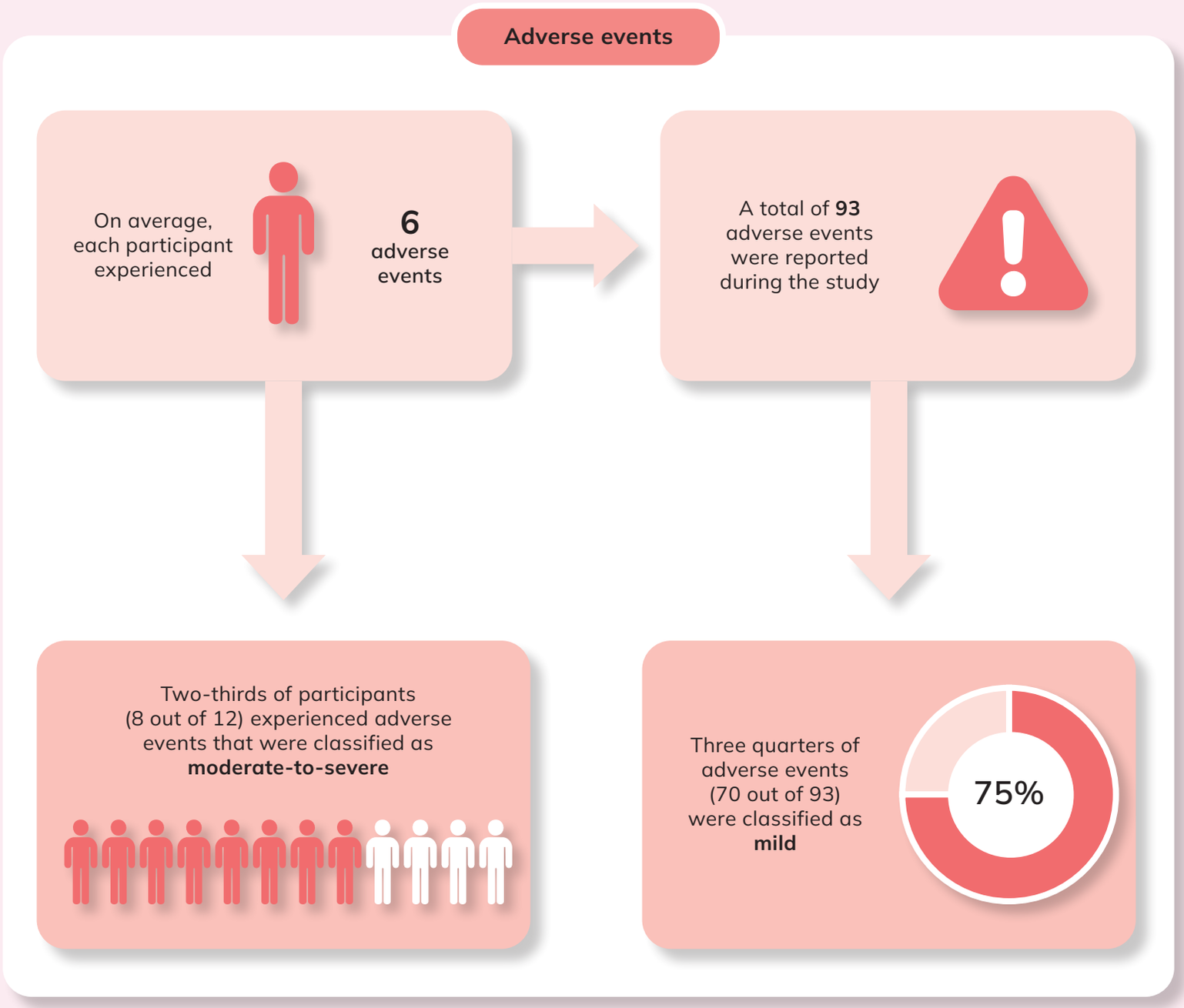
More frequent treatment was effective for participants who had surgery during the study

Three participants had surgery during either this study or their previous study. They received more frequent treatments during this time. They did not have any new lesions or lesions that came back.

Most of the adverse events that participants experienced were classified as mild

The researchers did not think that any of the mild, moderate, or serious adverse events experienced by participants in the study were related to treatment with IV PLG concentrate.



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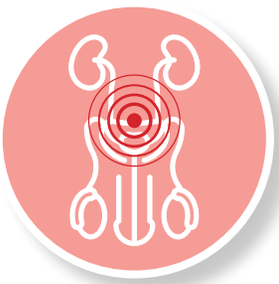
Most common adverse events

5 out of **12** participants had ear pain
(almost half)

4 out of **12** participants had strep throat (a throat infection)
(one-third)

3 out of **12** participants had abdominal (stomach) pain
(one-quarter)



3 out of **12** participants had an infection in the urinary system
(one-quarter)

3 out of **12** participants experienced fever
(one-quarter)

5 participants experienced a serious adverse event: 3 participants had COVID-19; 1 participant had an infection in their left kidney and the tube that carries urine (pee) from the kidney to the bladder (ureter); and 1 participant had problems with a small device implanted under their skin to provide long-term access to a vein (known as a Port-a-Cath).

Nobody died during the study. Nobody had to stop IV PLG concentrate treatment due to adverse events and nobody developed **neutralizing antibodies** against IV PLG concentrate, which would have stopped the treatment from working.

Neutralizing antibodies: Small proteins that are part of the immune system, which recognize and attach themselves to viruses and proteins and stop them working. Sometimes the immune system will produce neutralizing antibodies that stop certain medicines from working.

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What do the results mean?

Overall, long-term treatment with IV PLG concentrate is effective for people living with PLGD-1 and is well tolerated. New lesions tend to improve quickly with treatment, while older lesions may take a year or longer to improve. Everyone in this study was 39 years old or younger. People of all ages receiving IV PLG concentrate need to be carefully monitored to provide more information about treatment in different age groups.

Treatment with IV PLG concentrate can be tailored to meet people's individual needs. This is very important for people living with this ultra-rare condition.

Where can I find more information about the study described in this summary?

The original article appeared in a journal called *Haemophilia* with the title: 'Safety and efficacy of long-term treatment of type 1 plasminogen deficient patients with intravenous plasminogen replacement therapy'.

- https://doi.org/10.1111/hae.70019

You can read more about the study on the following website:

Type the following number NCT03642691 into the search bar of the ClinicalTrials.gov website at:

- https://www.clinicaltrials.gov/

If you were involved in the study and have questions about the registry or the analysis, please speak with your doctor.

More information on PLGD-1 can be found at:

- https://www.plasminogendeficiency.org/
- https://rarediseases.org/rare-diseases/congenital-plasminogen-deficiency/

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Disclaimers

This summary reports the results of a single study. The results of the study may differ from those of other studies. Healthcare professionals should make treatment decisions based on all available evidence, not on the results of a single study.

Author contributions

All authors were involved in the writing, reviewing, and editing of the summary, and approved the final version for publication.

Acknowledgements

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Ethics approval and consent to participate

The protocol was approved by the institutional review board or ethics committee at each study center. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice. All participants provided written informed consent, with assent obtained from children aged 7 to 17 years old.

Financial & competing interest disclosure

Amy D. Shapiro has acted as a clinical trial investigator for Prometic Biotherapeutics Inc. (currently Kedrion Biopharma Inc.), has received compensation paid directly to the Indiana Hemophilia & Thrombosis Center (IHTC) for consultation, speaker's bureau, or participation in advisory boards from Be Biopharma, BioMarin, Genentech/Roche, HEMA Biologics, Kedrion Biopharma Inc., Novo Nordisk, Pfizer, Sanofi-Genzyme/Bioverativ, has received research support from Centessa Pharmaceuticals/ApcinteX Ltd, Genentech/Roche, Kedrion Biopharma Inc., Novo Nordisk, Pharmacosmos A/S, Pfizer, Regeneron, Sanofi-Genzyme/Bioverativ and Takeda Pharmaceuticals, and sits on the board of the Novo Nordisk Haemophilia Foundation. Heather McDaniel has acted as a clinical trial investigator for Prometic Biotherapeutics Inc. (currently Kedrion Biopharma Inc.) and a paid consultant for Kedrion Biopharma Inc. Charles Nakar has received compensation from Prometic Biotherapeutics Inc. (currently Kedrion Biopharma Inc.) paid directly to the IHTC for honoraria, reimbursement for lectures, and research support. Joseph M. Parker was an employee of Prometic Biotherapeutics Inc. (currently Kedrion Biopharma Inc.) and received consultancy fees from Kedrion Biopharma Inc. Karen Thibaudeau is an employee of Prometic Bioproduction Inc. (doing business as Kedrion Biopharma Canada). Robert W. Decker, Jeremy Lorber, and Neelam Thukral report no conflict of interest. In addition, U.S. patent No.11,291,711 (Plasminogen Replacement Therapy for Plasminogen Deficiency) was originally held by Prometic Biotherapeutics Inc. and has since been transferred to Kedrion Biopharma Inc.

Author contributions for the original article

A statement on author contributions is available with the full text of the original article published in *Haemophilia*: https://doi.org/10.1111/hae.70019

Availability of data and materials

A data-sharing statement provided by the authors is available with the full text of the original article published in *Haemophilia*: https://doi.org/10.1111/hae.70019