

## Leniolisib treatment for people with activated PI3K delta syndrome (APDS): a plain language summary of the phase 3 study

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

- The full name of the clinical study described in this summary is “Study of Efficacy of CDZ173 in Patients With APDS/PASLI”.
- The original article reporting on this clinical study, titled “A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome”, was published in the scientific journal *Blood* in 2023. You can read the original article for free at: <https://ashpublications.org/blood/article/141/9/971/493284/A-randomized-placebo-controlled-phase-3-trial-of>. The article DOI is: <https://doi.org/10.1182/blood.2022018546>
- You can read more about how the study was designed and carried out on the ClinicalTrials.gov website at: <https://clinicaltrials.gov/study/NCT02435173>.

### Summary

#### What is this summary about?

This is a plain language summary of an article originally published in *Blood*. Leniolisib is a drug developed to treat activated PI3K delta syndrome (APDS). APDS is a rare disease in which the immune system does not work correctly. People with APDS have a wide range of symptoms including infections, certain organs associated with the immune system becoming larger, and worse quality of life. This summary reports the results from a clinical study that aimed to understand if leniolisib is effective at treating people with APDS.

#### What were the results?

The study showed that leniolisib improved the amounts of immune cells and antibodies (proteins that help the immune system to function). Leniolisib also reduced the size of participants' enlarged organs, and lowered the activity of the protein that causes APDS. There were no major safety concerns for participants who took leniolisib.

#### What do the results mean?

These results indicate that leniolisib helps the immune system to work in a way that is closer to those without APDS. By helping the immune system, leniolisib may be able to improve the lives of people with APDS by making them feel better. Leniolisib may also prevent difficulties in completing activities in the daily lives of people with APDS.

How to say (double-click on the icon to play sound)...

- **Activated PI3K delta syndrome:**  
AK-tih-vay-tid PEE-eye-three-KAY DEL-tuh sin-DROHM
- **Leniolisib:** len-EE-ol-iss-ib

### Who funded this study?

This study was **sponsored** by Novartis and Pharming Group N.V.

**Sponsor:** A sponsor is a company organisation that oversees and pays for a clinical research study. The sponsor also collects and analyses the information that was generated during the study.



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## Who should read this article?

This article is intended for people with APDS, their family members and caregivers, and healthcare professionals. This article contains information about a clinical study that investigated a new treatment for APDS called leniolisib.

## What is the immune system?

The immune system:

- Protects the body against infections from outside invaders, like bacteria and viruses, and fights off any infections that have started to spread.
- Protects the body and prevents sickness when its own cells are weakened or damaged.
- Is made up of a collection of cells, organs, and **tissues**.

### Immune system organs

**Primary lymphoid organs:** where new immune cells are produced and begin to develop

**Thymus:** where different types of immune **T cells** are first made

**Bone marrow:** where different types of immune **B cells** are first made

**Secondary lymphoid organs:** where immune cells are activated and multiply in response to an infection, which triggers an immune response

**Tonsils:** small organs in the back of the throat. Tonsils help to filter substances entering the body that may cause infection

**Lymph nodes:** small bean-shaped organs throughout the body. Lymph nodes filter substances and contain immune cells to help the body fight infection

**Lymphatic vessels**

**Liver**

**Spleen**

**Lymphatic vessels:** a collection of tubes which move immune cells around the body and connect the different parts of the immune system together

**Liver:** an organ that filters substances coming from the stomach that may cause infection

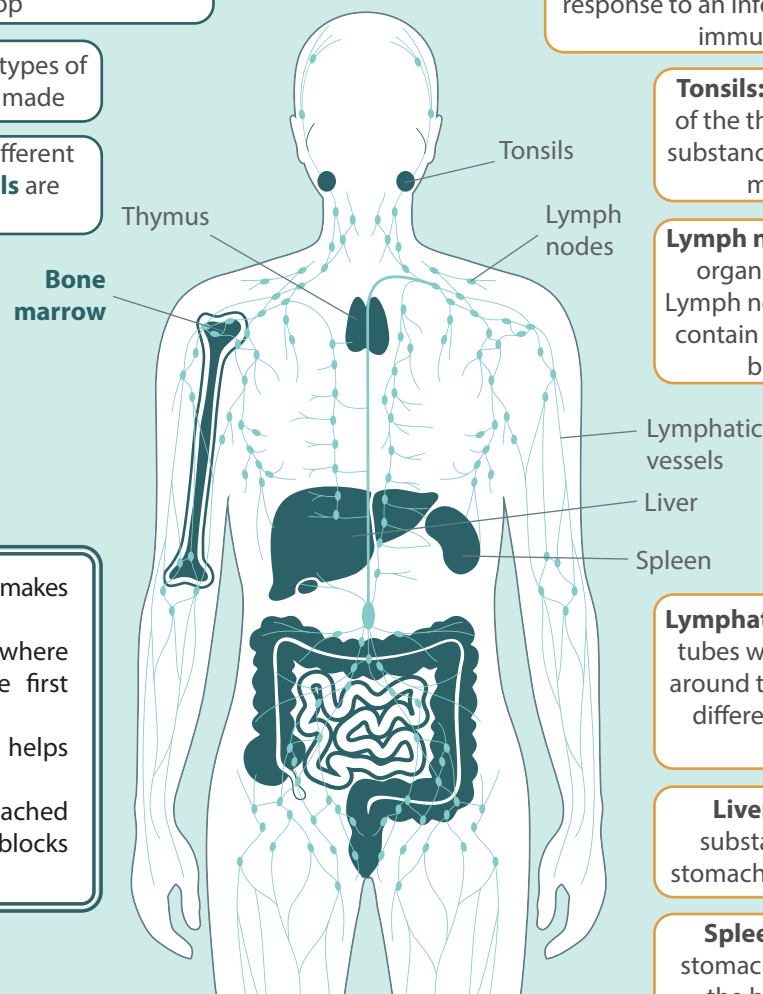
**Spleen:** an organ above the stomach that fights infections in the blood and removes old, damaged blood cells

**B cell:** a type of immune cell that makes **antibodies** to fight infections.

**Bone marrow:** a part of the bone where blood cells and immune cells are first made.

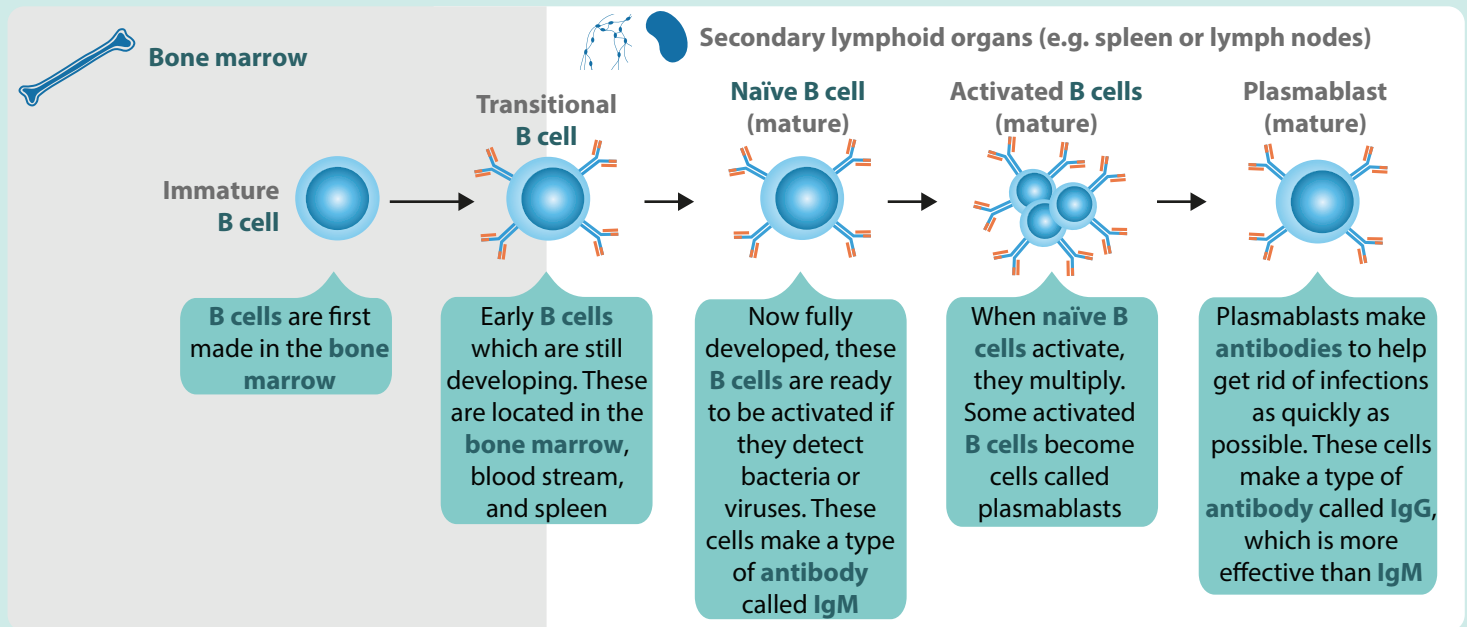
**T cell:** a type of immune cell that helps fight infections.

**Tissue:** a group of different cells attached together. Tissues are the building blocks for organs.

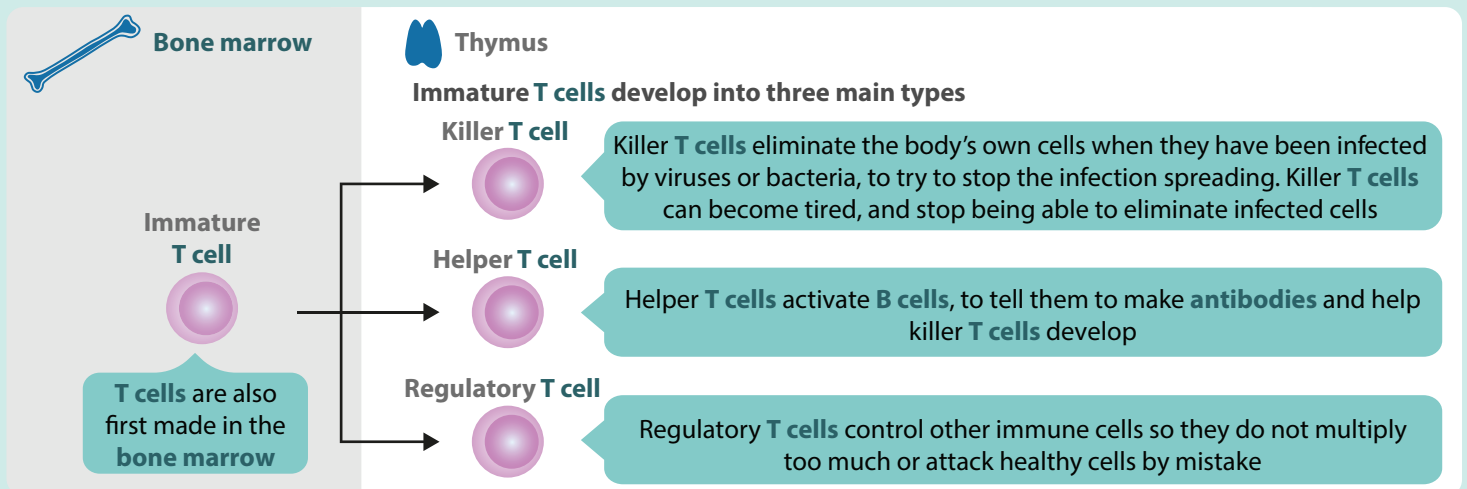


There are many types of immune cells which help protect the body from infections in different ways. Two important groups of immune cells are **B** and **T** cells.

### B cell development process



### T cell development process



#### Antibodies:

- Antibodies are substances which are made by **B cells**. Antibodies attach to bacteria or viruses to identify them as harmful. Cells from the immune system can then identify the bacteria and viruses and destroy them to get rid of an infection.
- When **B cells** first detect bacteria or viruses, they make a type of antibody called **IgM**. **IgMs** do not attach to bacteria or viruses very tightly, so they might fall off the bacteria or virus before immune cells can remove them.
- When **B cells** turn into plasmablasts, they make more effective antibodies which attach to bacteria and viruses more strongly. An example of a more effective antibody is **IgG**. These antibodies are better than **IgM** at getting rid of infections.

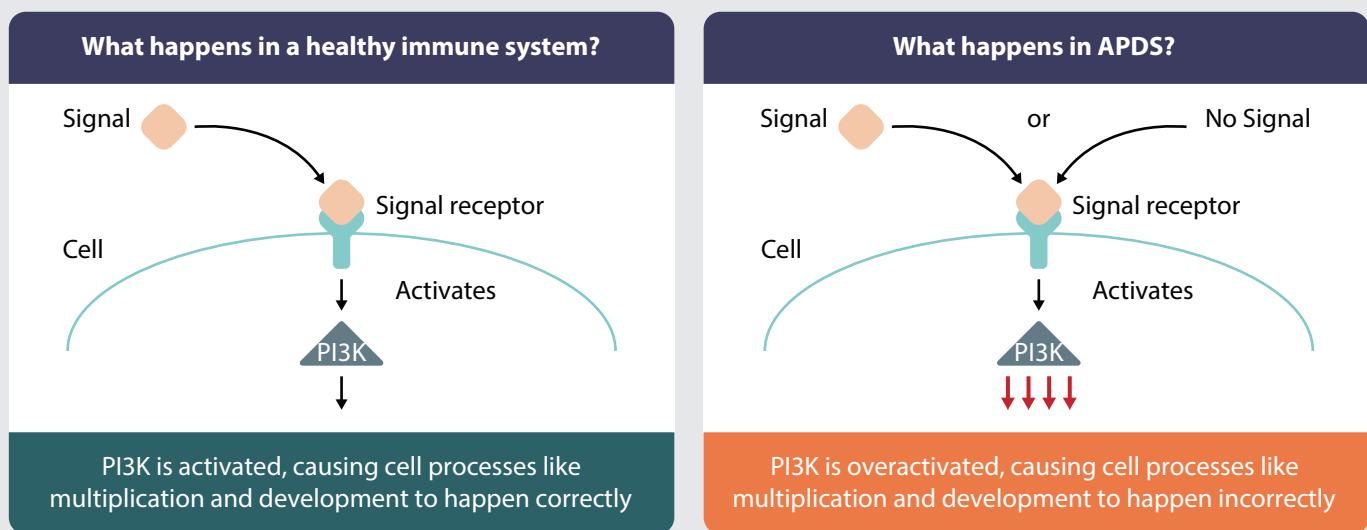
**IgM, IgG:** these stand for immunoglobulin M and immunoglobulin G. Immunoglobulin is another word for **antibody**, and G and M are types of **antibody** which play different roles in immunity.

**Naïve B cell:** a mature **B cell** that has not yet been activated.

## What is APDS?

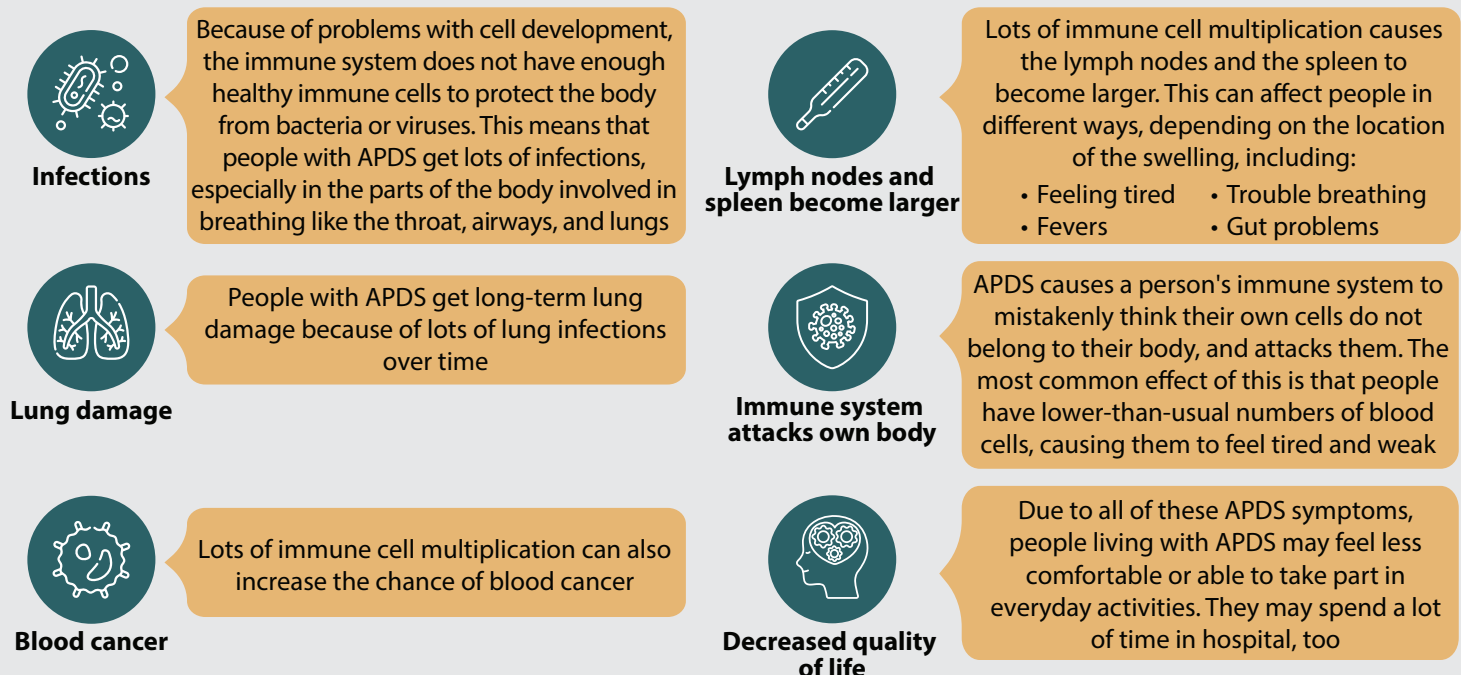
- APDS is a disease where cells of the immune system do not work correctly. APDS stands for Activated Phosphoinositide 3-kinase Delta Syndrome. APDS is caused by changes or mistakes in genes which contain the instructions for the body to make a protein called PI3K delta.
- APDS is a very rare disease. At the moment, fewer than 1 out of every 1 million people are known to live with APDS, however this number may be an underestimate due to low awareness of APDS.
- In APDS, data show that PI3K delta causes cell processes to happen more intensely than in the healthy immune system (this is called overactivation). These processes happen both with and without the usual signal that is usually needed to trigger them. This causes problems with cell development and can cause too much cell multiplication.

### Effect of APDS on the immune system



As the immune system cannot work correctly, people with APDS experience lots of different symptoms.

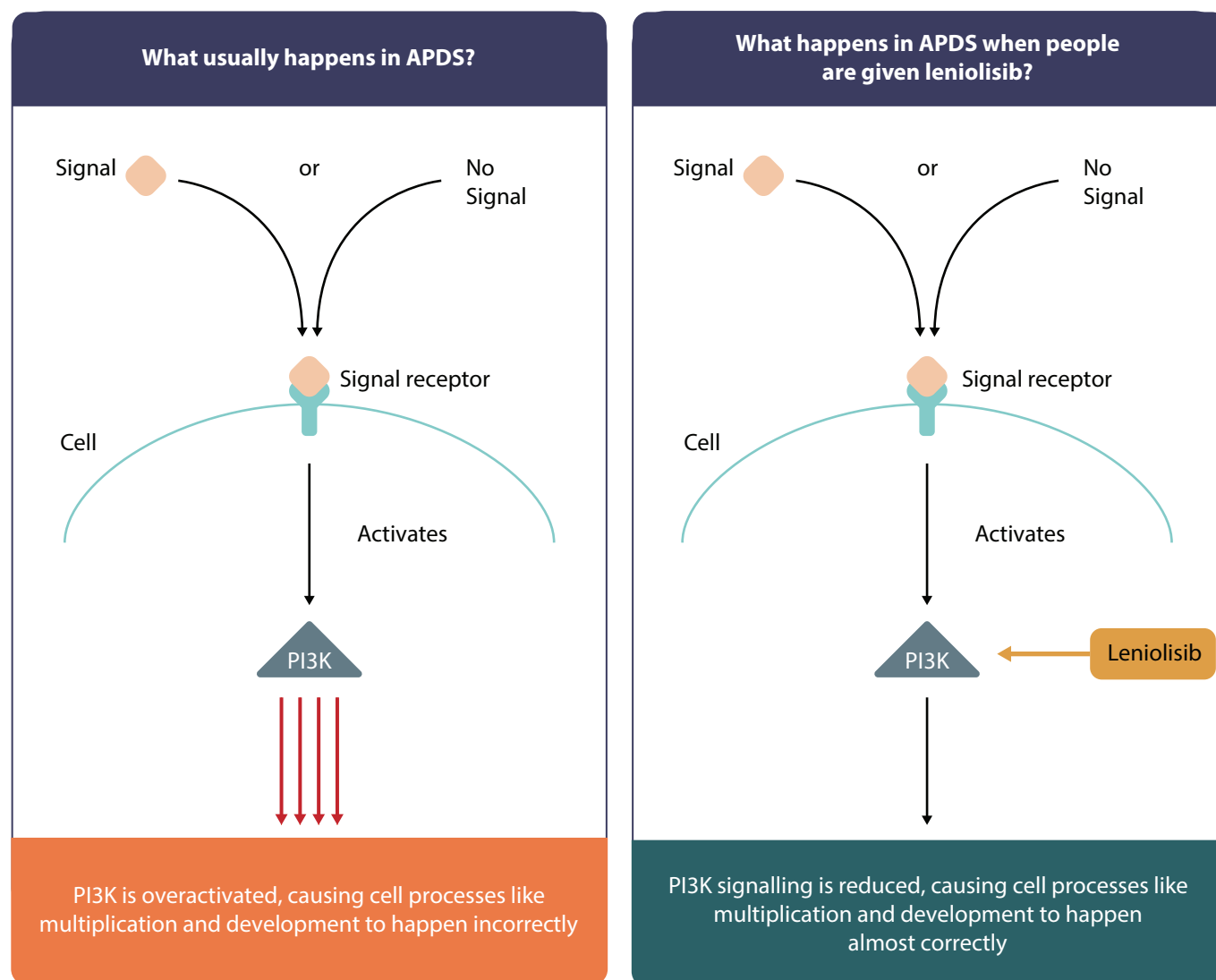
### APDS symptoms



## What is leniolisib and how does it work?

Leniolisib is a drug being developed to treat people with APDS. Leniolisib is taken as a tablet, twice a day (once in the morning and once in the evening). Leniolisib reduces the ability of PI3K delta to send signals, which means PI3K delta signalling goes back to a healthy level. This can help cell processes like multiplication and development to happen almost in the same way as in healthy immune systems.

### Effect of leniolisib treatment on the immune system

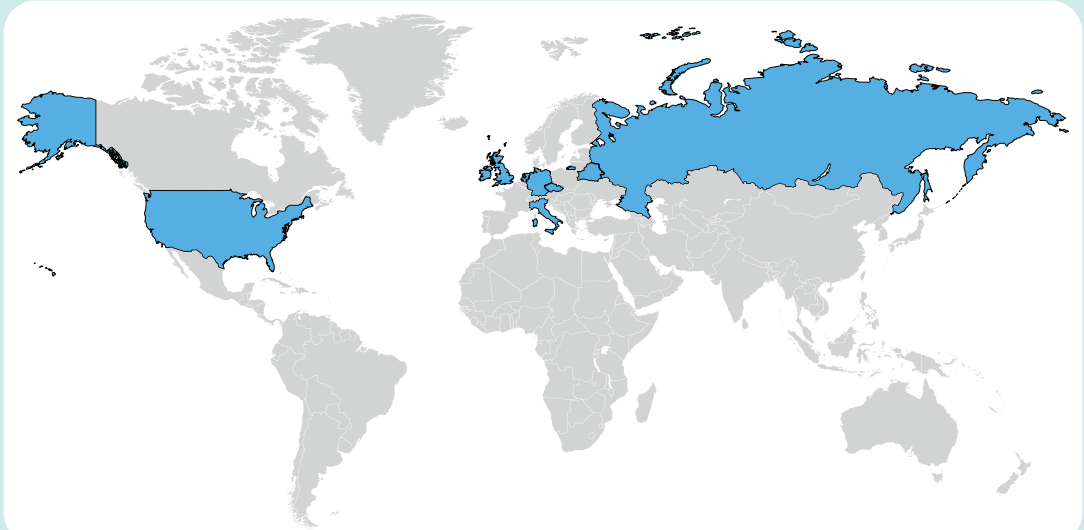


By returning PI3K delta signalling to a healthy level, leniolisib may be able to reduce the symptoms experienced by people with APDS. The effect of leniolisib on APDS was investigated in the **phase 3 study**.

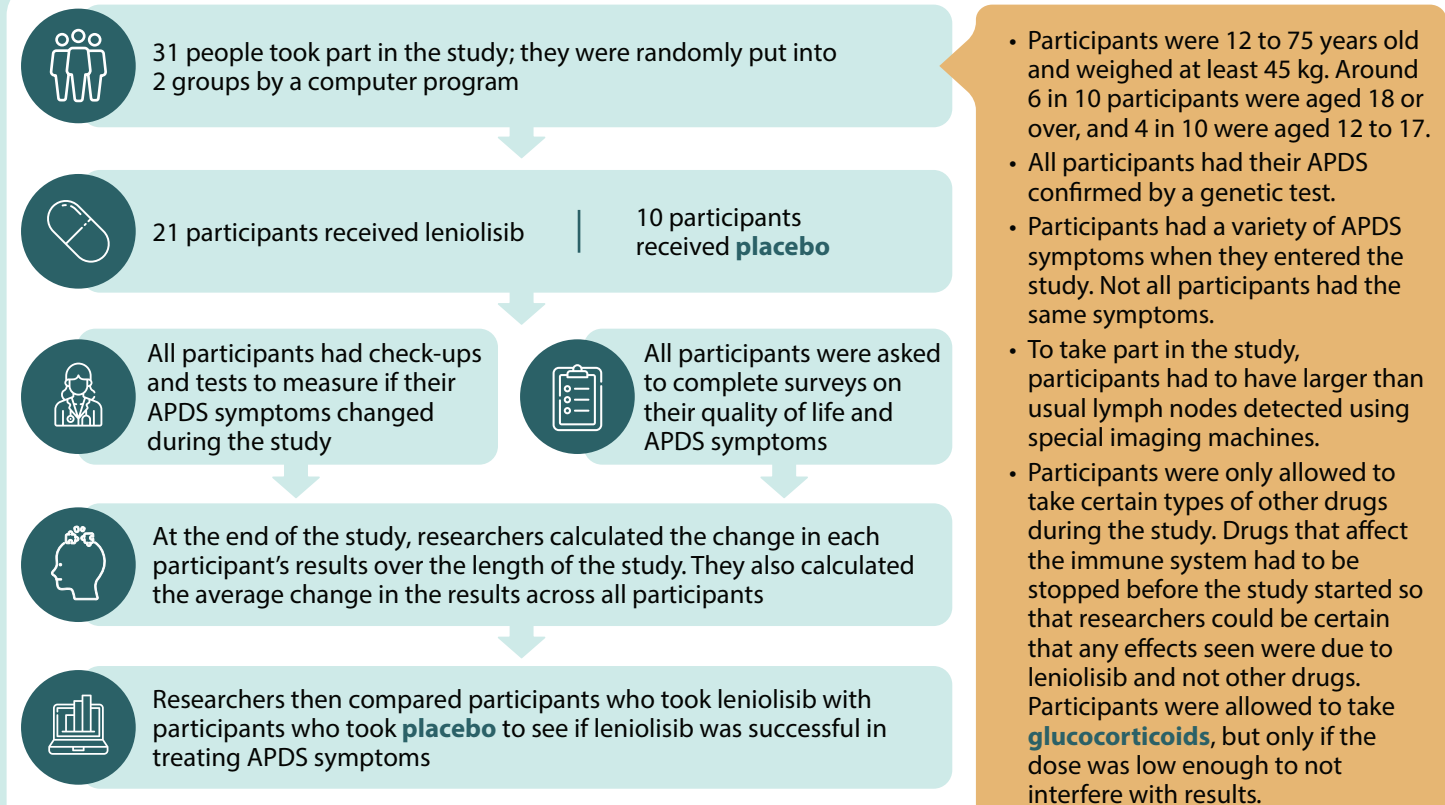
**Phase 3 study:** gathers data on whether a drug works in people with a specific disease, and if people have any side effects while taking it. Earlier phases may use healthy participants, but Phase 3 studies use patients with the specific disease.

## How was this study carried out?

- The **Phase 3 study** investigated whether leniolisib could be used to treat people with APDS.
- The study took place in nine countries: Belarus, the Czech Republic, Germany, Ireland, Italy, the Netherlands, the Russian Federation, the United Kingdom, and the USA.



## What happened during the study?



**Glucocorticoids:** a type of steroid, which are drugs used to treat inflammation and immune system disorders.


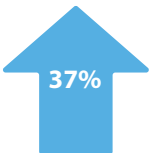
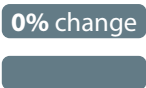







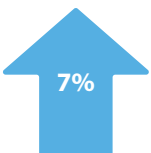
**Placebo:** looks like the study drug but has no study drug in it. Comparing a drug to a placebo helps researchers to be sure that changes are because of the study drug and did not happen by chance.

## What were the results?

### Measuring numbers of immune cells and antibodies

Researchers aimed to prove that leniolisib treatment had an effect on the amounts of different immune cells. To do this, researchers looked at blood samples from participants and used special equipment to count the numbers of different immune cells. At the end of the study, they found that the number of **naïve B cells** had increased by 37% more in participants who took leniolisib than in those who took **placebo**. These changes were **statistically significant**.

### Immune cell and antibody level results

Immune cell or antibody	What happens in APDS?	What happened when participants took leniolisib?	What happened when participants took placebo?	What do these changes mean?
Naïve B cells				Returning to a healthy amount of <b>B cells</b> may help the immune systems of participants to work more correctly. This will mean that they are better at fighting infections
Transitional B cells				
IgM antibodies				Lower levels of <b>IgM</b> may mean that more effective antibodies, such as <b>IgG</b> , are being made instead. If participants have larger amounts of more effective <b>antibodies</b> , their immune systems will be better at fighting the bacteria and viruses that have entered their body
Regulatory and helper T cells				With more helper and regulatory <b>T cells</b> , the immune system may be able to act like the healthy immune system and be better at fighting infections

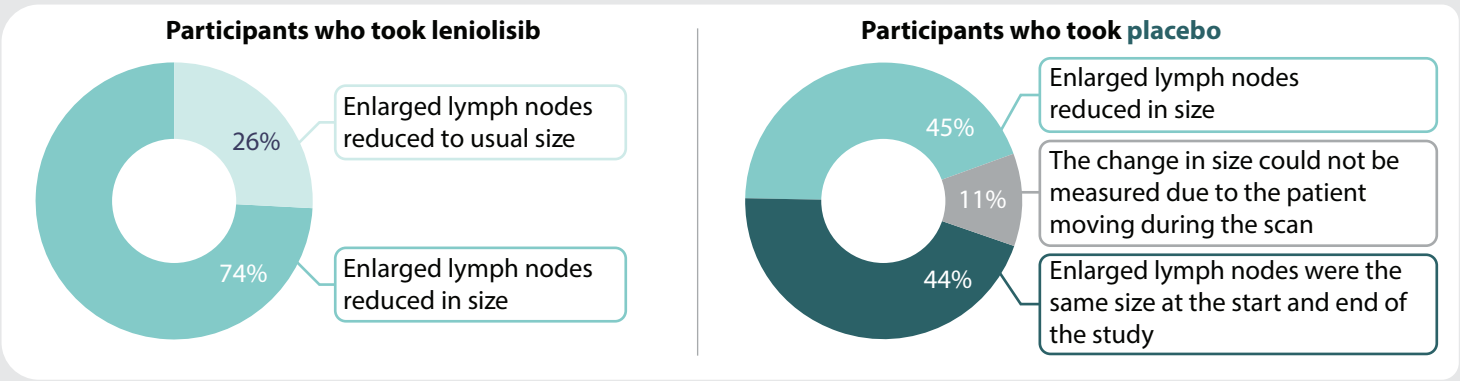
**Statistically significant:** When a result is statistically significant, it means that it is very likely that the difference between the result in participants who took the study drug and in those who took **placebo** is because of the effect of the study drug, and not by chance. Statistical significance is based on calculations done by researchers.



Measuring enlargement of lymph nodes and spleen

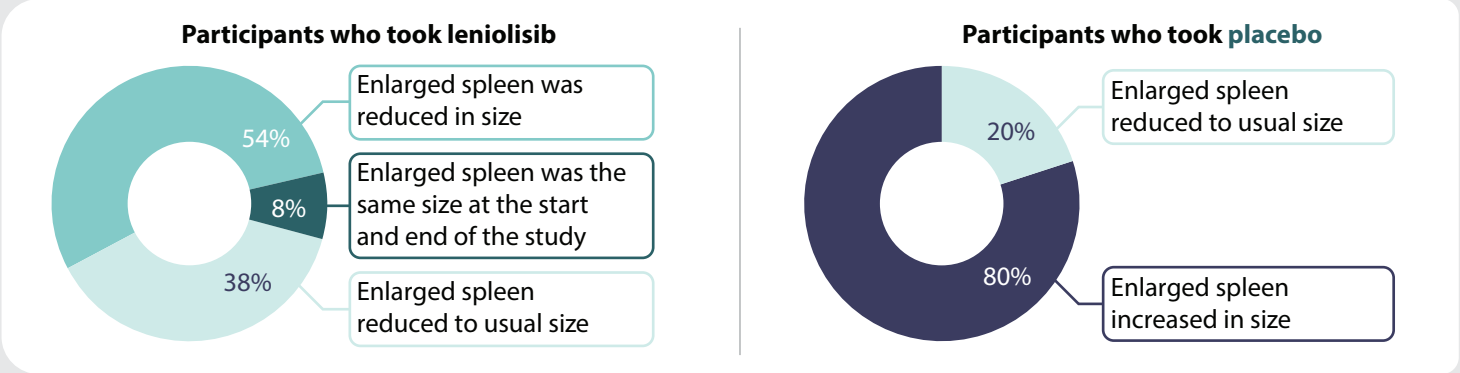
- In APDS, immune cells multiply and can cause the organs that store immune cells (lymph nodes and spleen) to become larger. To measure the size of these organs and see how much their size had increased, the researchers took images using special imaging machines: either computed tomography (CT) or magnetic resonance imaging (MRI) scanners.
- The researchers found that the size of the largest lymph nodes decreased 41% more in participants who took leniolisib than in those who took **placebo** (lymph node size decreased by 46% in participants receiving leniolisib and 5% in participants receiving **placebo**). These changes were **statistically significant**.
- A bigger proportion of participants who took leniolisib had improvements in their enlarged lymph nodes at the end of the study than participants who took **placebo**. Improvement in this case meant either a reduction or no further increase in size.

Proportion of participants who had changes in enlarged lymph node size



The spleens of participants who took leniolisib reduced in size more than the spleens in the group who took **placebo**. The spleen size was 14 cm<sup>2</sup> smaller in participants who took leniolisib compared to participants who took **placebo**. These changes were **statistically significant**.

Proportion of participants who had changes in enlarged spleen size, among those who had an enlarged spleen at the start of the study



Reductions in the size of the organs that store immune cells suggest that immune cells were multiplying less than they were before participants started leniolisib treatment. This may improve symptoms of people with APDS.



## Safety results

- To decide if leniolisib is safe for people with APDS to take, all side effects were recorded. Side effects were any unwanted symptoms during the study, and may or may not have been caused by the treatments used in the study. None of the side effects caused participants to stop taking part in the study and no participants died.

## Side effects experienced during the study

### The most common side effects in participants who took leniolisib were:

- Hair loss
- Mouth sores
- Food and drink tasted different
- Threw up
- Increased weight

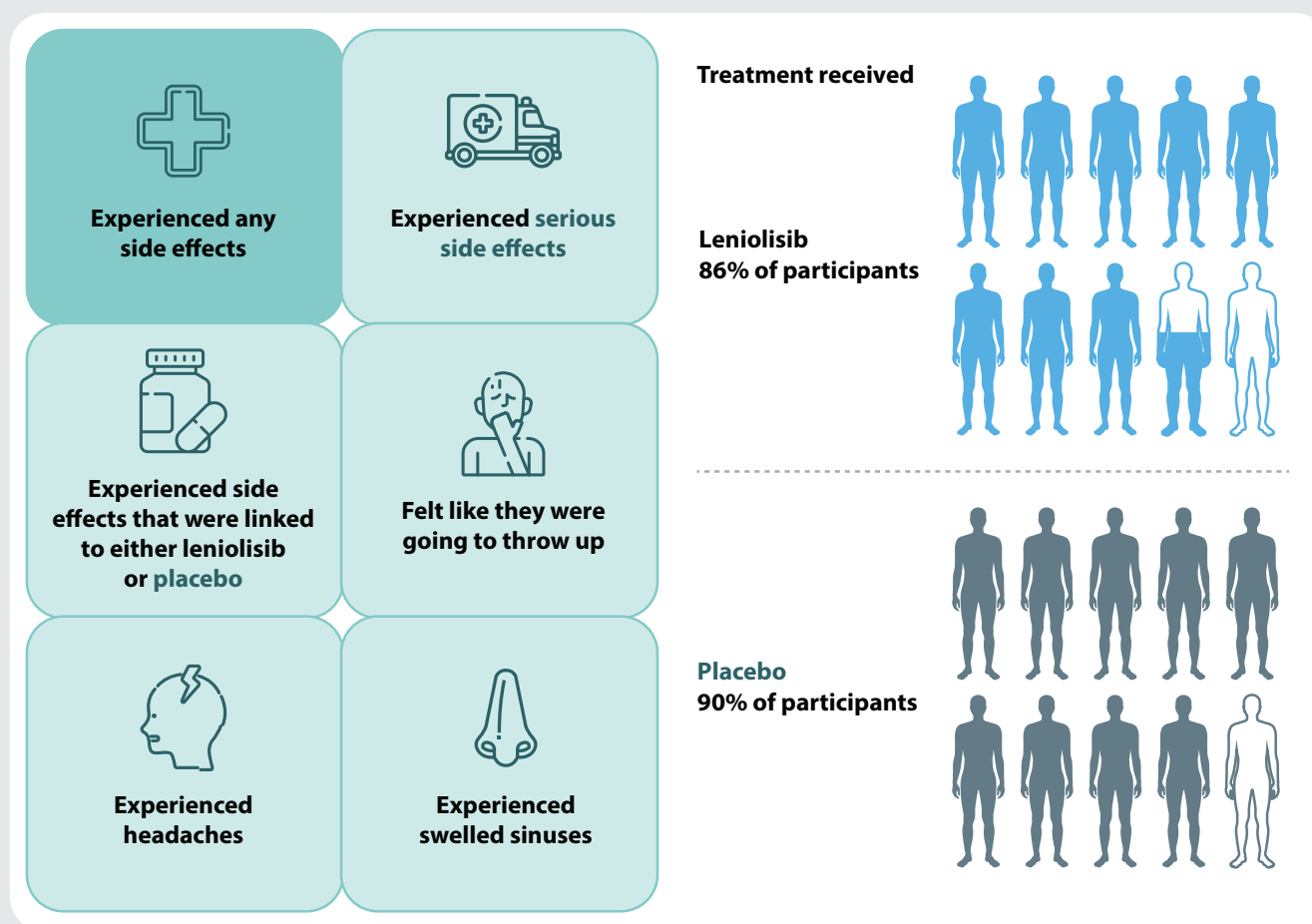
### The most common side effects in participants who took placebo were:

- Stomach pain
- Difficulty breathing
- Feeling tired
- Headaches
- Inflammation of the blood vessels
- Dizziness

### Other side effects recorded were:

- One participant who took leniolisib had a rash that had both flat and raised parts
- Four participants who took leniolisib had low numbers of neutrophils, (which are a type of immune cell) at the end of the study. However, it did not lead to any symptoms

**Serious side effect:** a serious side effect is one that could be life-threatening, that needs to be treated in hospital, or that causes lasting problems.





Experienced any side effects



Experienced serious side effects



Experienced side effects that were linked to either leniolisib or placebo



Felt like they were going to throw up

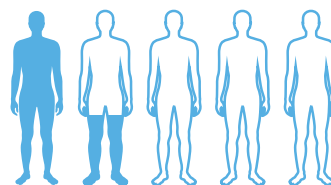


Experienced headaches

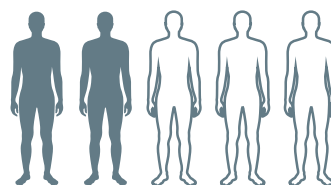
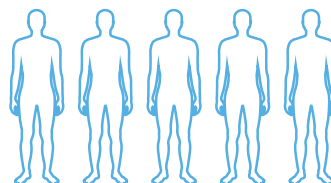


Experienced swelled sinuses

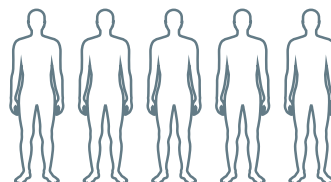
Treatment received



Leniolisib  
14% of participants



Placebo  
20% of participants



Experienced any side effects



Experienced serious side effects



Experienced side effects that were linked to either leniolisib or placebo



Felt like they were going to throw up

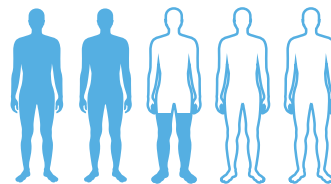


Experienced headaches

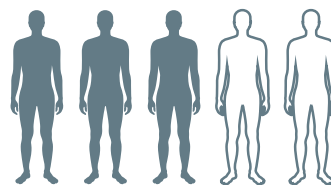
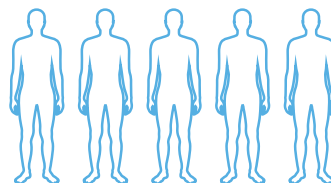


Experienced swelled sinuses

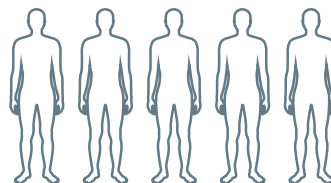
Treatment received



Leniolisib  
24% of participants



Placebo  
30% of participants





**Experienced any  
side effects**



**Experienced serious  
side effects**



**Experienced side  
effects that were linked  
to either leniolisib  
or placebo**



**Felt like they were  
going to throw up**

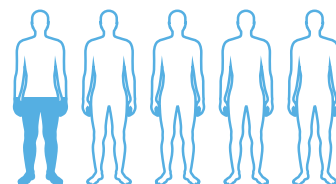


**Experienced  
headaches**

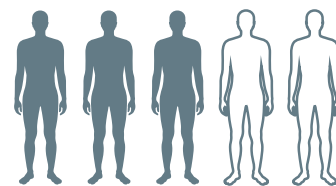
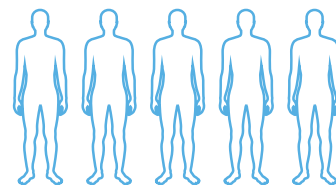


**Experienced  
swelled sinuses**

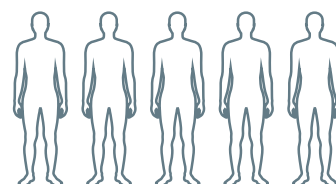
**Treatment received**



**Leniolisib  
5% of participants**



**Placebo  
30% of participants**



**Experienced any  
side effects**



**Experienced serious  
side effects**



**Experienced side  
effects that were linked  
to either leniolisib  
or placebo**



**Felt like they were  
going to throw up**

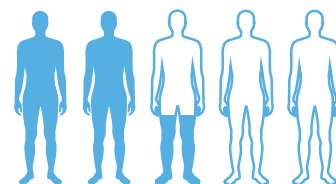


**Experienced  
headaches**

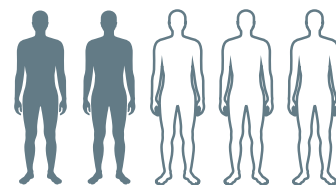
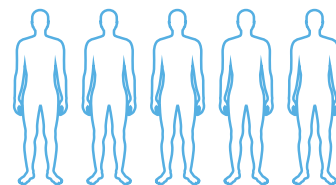


**Experienced  
swelled sinuses**

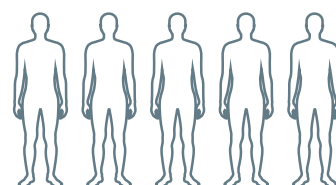
**Treatment received**

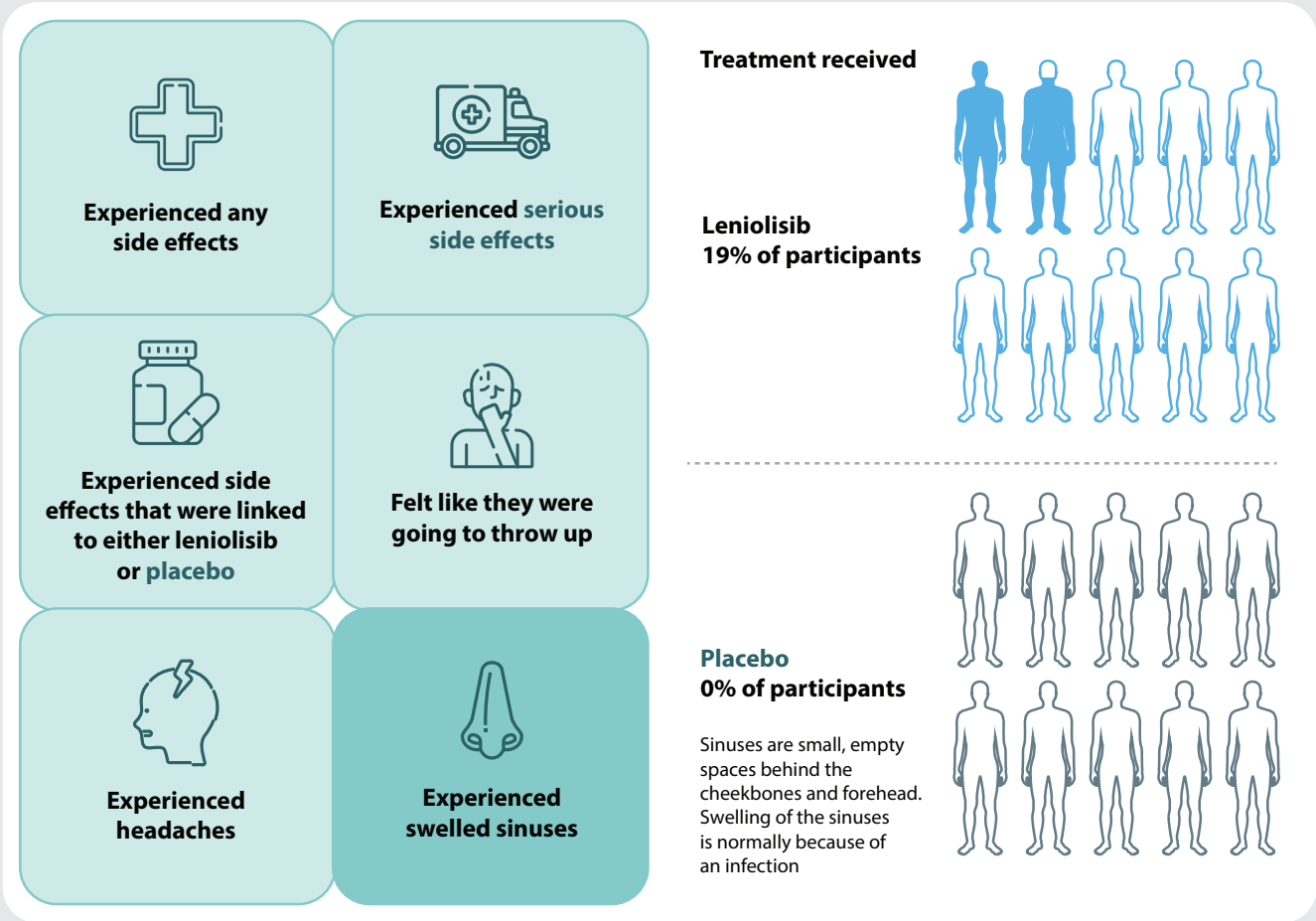


**Leniolisib  
24% of participants**



**Placebo  
20% of participants**





# Patient- and researcher-reported outcomes

- All the participants and the researchers running the study answered questions about the impact of APDS on participants' health, at both the start and end of the study.

Questionnaire	What does the questionnaire ask?	Did answers show an improvement at the end of the study for participants who took leniolisib?	Did answers show an improvement at the end of the study for participants who took placebo?	How big was the difference between the effect of leniolisib and placebo?
<b>Physician's general assessment</b>	Researchers answered an APDS-specific question on how well a participant was and if they had less symptoms at the end of the study	<b>Yes</b> Participants had reduced symptoms	<b>Yes</b> Participants had reduced symptoms	The differences in answers were quite small and were <b>not statistically significant</b> . This means it is not possible to know if the different answers were because some participants took leniolisib and some took <b>placebo</b> , or if there were other reasons
<b>Patient general assessment</b>	Participants answered an APDS-specific question on how well they felt	<b>Yes</b> Some improvements in participant wellbeing	<b>No</b>	
<b>36-Item Short Form Survey</b>	Participants answered questions on their quality of life, including their physical and mental health	<b>No</b>	<b>Yes</b> Improvements in physical function only	
<b>Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire</b>	Participants answered questions about if they could take part in their normal school, work, or daily activities	<b>Yes</b> Some improvements in ability to take part in school, work and/or daily activities	<b>No</b>	

In addition to answering questionnaires, researchers in the study also reported how the participants seemed in general. By the end of the study, 7 in 10 participants who took leniolisib were able to do more exercise and felt less tired, whereas only around 4 in 10 participants who took **placebo** were able to do more exercise and felt less tired.

## What do the results mean?

- This was the first clinical study to learn about the safety and effects of leniolisib in people with APDS. In this study, leniolisib was better than **placebo** at:
  - Improving the amounts of immune cells and **antibodies**.
  - Reducing the size of the immune organs (lymph nodes and spleen) that had become larger due to APDS.
- These results may mean that leniolisib lowers the activity of PI3K delta, the protein that causes APDS, and helps the immune system to work closer to those who do not have APDS.
- By helping the immune system to work correctly, leniolisib may be able to improve APDS symptoms, for example, reducing how many infections people get, stopping long-term lung damage, and reducing the risk of cancer. Leniolisib might help people with APDS to feel better and prevent difficulties in completing activities in their daily lives.
- Researchers did not find any major safety concerns.
- These are the results of a single study. Other studies may show different results. As APDS is a rare disease, the number of participants in this study was low. The study was also short compared to other **Phase 3 studies**. This means that the results show what APDS might do, rather than what it will do. Researchers need to conduct more studies to look at the effects of leniolisib in more people and over a longer period of time.

## Where can I find out more about APDS?

For more information on APDS, including links to national charities and patient associations with a focus on APDS, please go to [apdsandme.eu](https://apdsandme.eu) or speak to your healthcare provider.

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### Competing interests disclosure

E. Kulm is an employee of Leidos Biomedical Research, Inc. S. Webster is a consultant for Pharming Group N.V. A. Šedivá is a consultant for Octapharma, Takeda, and Pharming Group N.V. and lecturer for CSL Behring. V.A.S.H. Dalm is a consultant for and/or receives honoraria from AstraZeneca, Kedrion, Takeda, CSL Behring, Pfizer, and Pharming Group N.V. V.A.S.H. Dalm also receives honoraria from Pfizer, and research funding from Takeda. J. Körholz received travel expenses and honoraria from Pharming. J. Bradt and J. Luscombe are current employees and stock option holders of Pharming Group N.V., and J. Bradt holds individual stock in NeoClone. The remaining authors declare no competing financial interests. The authors have no other competing interests or relevant affiliations with any organization or entity with regard to the subject matter or materials discussed in the manuscript apart from those disclosed.

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