Plain Language Summary of Publication

Future Rare Diseases

Spesolimab treatment for the prevention of flares in people with generalized pustular psoriasis (GPP): a plain language summary of the Effisayil™ 2 study

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Summary

What is this study about?

Generalized pustular psoriasis (shortened to GPP) is a rare, potentially life-threatening disease in which pus-filled blisters or pustules may suddenly form all over the body. The drug **spesolimab** has been approved to treat worsening GPP (known as flares) in many countries. However, it was not known if **spesolimab** could prevent the symptoms of GPP. This summary reports the results from a clinical study called Effisayil™ 2, that was done to understand if **spesolimab** was a safe and effective way to prevent flares in people with GPP. In the study, 123 participants, recruited in 20 different countries, were given one of three different doses of **spesolimab** (low, medium, or high) or a non-active medicine (placebo) over 48 weeks.

How to say (double-click to play sound)...

- **Spesolimab:** spess-OH-lee-mab
- **Generalized pustular psoriasis:** JEH-neh-ruh-lized puss-TUH-lar suh-RY-uh-sis

What were the results?

Participants who received **spesolimab** had fewer GPP flares over the course of the 48-week study. Different doses of the drug were tested and compared to placebo, and a high dose of **spesolimab** worked better than low and medium doses. Using **spesolimab** also reduced the chance of developing skin symptoms, such as redness or pustules, and prevented quality of life getting worse over 48 weeks. While some participants experienced unwanted effects, they were mostly mild or moderate and most did not appear to be caused by **spesolimab**, or the dose at which it was given.

What do the results of the study mean?

The results indicate that a high dose of **spesolimab** works well to prevent GPP flares and stop the disease getting worse. Health authorities are looking at the results of this study to decide if **spesolimab** can also be prescribed for the prevention of GPP flares.

Who should read this article?

This summary is intended for people with GPP and their caregivers, patient advocates, and healthcare professionals, including those who are helping people find the best treatment for GPP.

Who sponsored this study?

This study was sponsored by Boehringer Ingelheim.

Sponsor: A sponsor is a company or 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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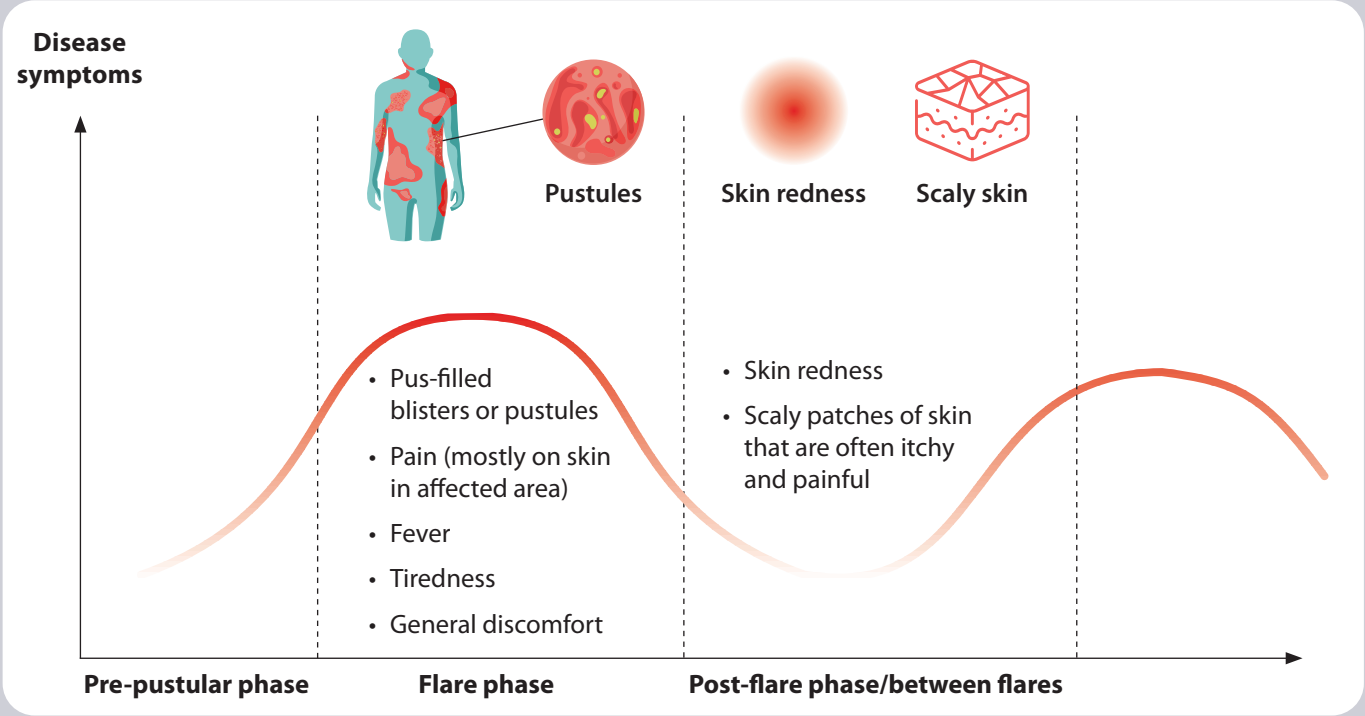
Where can I find the original article on which this summary is based?

The original article discussed in this plain language summary of publications (PLSP), titled "Efficacy and safety of subcutaneous **spesolimab** for the prevention of generalized pustular psoriasis flares (Effisayil 2): a multicenter, randomized, placebo-controlled trial" was published in *The Lancet* in 2023. You can read the abstract of the original article for free and the full article for a fee at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01378-8/fulltext

What is generalized pustular psoriasis (GPP)?

- GPP is a rare, unpredictable, lifelong disease in which the immune system mistakenly attacks healthy skin, causing pustules.
- During episodes of disease worsening, known as flares, pus-filled blisters or pustules may suddenly form anywhere on the skin.
- When patients experience a flare, the levels of a molecule called interleukin-36 (shortened to IL-36) increase. It is the increase in this molecule that is responsible for increased inflammation in the skin leading to painful pustules on the skin, and other potentially life-threatening complications such as sepsis and multisystem organ failure.
- Symptoms of GPP include pain (mostly on the skin in affected areas), fever, tiredness, and a general feeling of discomfort.
- GPP can also have a serious impact on social relationships and mental health, and many patients with the disease are diagnosed with depression and anxiety.
- Patients may have multiple GPP flares every year or there may be many years between flares.
- How bad the symptoms are can vary between each patient, and between each flare. Some flares are medical emergencies, and are serious enough that patients need to go to the hospital.
- Even when patients are not having a flare, GPP can still negatively impact their lives. Most patients continue to experience symptoms between flares including skin redness and scaly patches of skin that are often itchy and painful.



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What is spesolimab and how does it work?

- **Spesolimab** is a medication designed to attach to the IL-36 receptor and stop the IL-36 molecule causing inflamed skin and pustule formation.
- In a previous study called Effisayil™ 1, blocking IL-36 by injecting **spesolimab** into a vein in the arm of a patient who was having a flare stopped the flare and led to skin returning to normal or made the flare less severe.

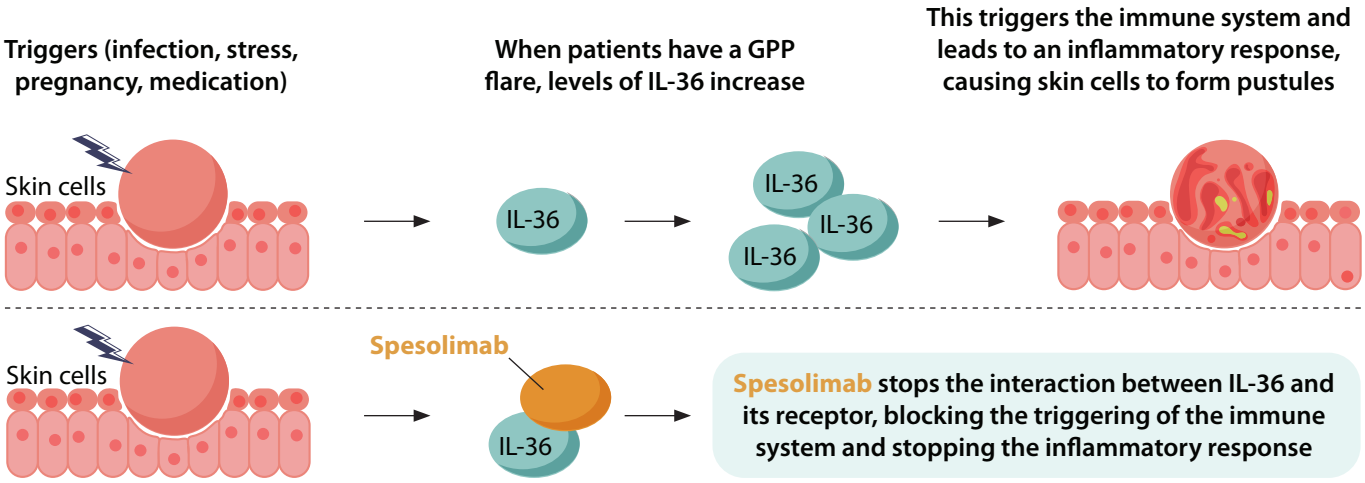


Figure reproduced with permission from Choon SE, Marrakchi S, Burden AD *et al.* Spesolimab treatment for people with flares of generalized pustular psoriasis: a plain language summary of the Effisayil™ 1 study. *Future Rare Diseases*. 2(2) (2023).

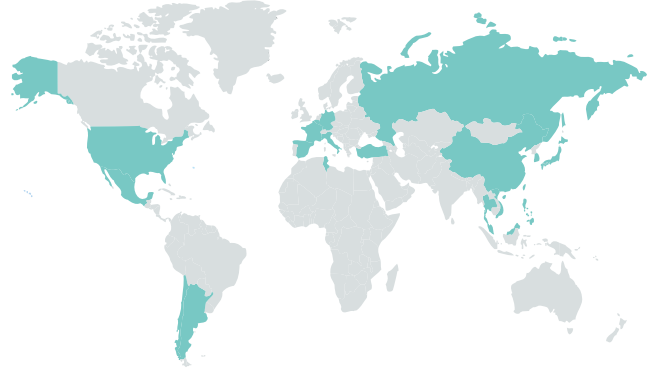
- Data from the Effisayil™ 1 study were important for the recent approval of **spesolimab** to treat GPP flares in patients living in Europe and several countries around the world, including the US, Canada, Japan, Taiwan, and China.
- Despite this advancing treatment of flares when they happen, there are still no therapies approved to prevent flares from happening.

What is the Effisayil™ 2 study and who took part?

- Effisayil™ 2 was a phase 2 clinical trial to investigate how effective and safe **spesolimab** was at preventing flares in participants with GPP aged between 12 and 75 years.
- A phase 2 study gathers data on whether a drug works in people with a specific disease and if participants have any unwanted effects while taking it.

The study took place in 60 specialist centres in 20 countries around the world:

Argentina (1 specialist centre), Belgium (1), Chile (1), China (7), France (2), Germany (7), Italy (1), Japan (6), Malaysia (8), Mexico (1), Philippines (3), Republic of Korea (1), Russia (5), Spain (1), Taiwan (2), Thailand (3), Tunisia (4), Turkey (3), the USA (1), and Vietnam (2).



How was the study carried out?

This was a **blinded study** in that participants did not know whether they were being given a non-active "dummy" medicine (placebo), low dose, medium dose, or high dose of the drug; the doctors were also not aware.

Blinded study: A study in which participants and doctors are not aware of the treatment they are receiving/giving. This prevents participants knowing which treatment they are receiving potentially influencing how they felt or reported their symptoms. It also prevents raising the doctors' hopes and expectations from influencing the results of the trial.

123 participants took part in the study

Participants were put randomly into four groups.

Both the doctor and the participant knew that **spesolimab** was the study medication.

Study length	Placebo	Low dose	Medium dose	High dose
Day 1	31 participants were given an initial dose of a non-active medicine (placebo), followed by a dose of placebo every 4 weeks	31 participants were given an initial medium dose of **spesolimab**, followed by a low dose of spesolimab every 12 weeks	31 participants were given an initial high dose of **spesolimab**, followed by a medium dose of spesolimab every 12 weeks	30 participants were given an initial high dose of **spesolimab**, followed by a medium dose of spesolimab every 4 weeks

Participants could receive an additional dose of **spesolimab** intravenously (meaning it is given by injection into a vein in the arm) if they experienced a GPP flare, and another dose if they continued to experience symptoms of a flare

Week 4 to 44

Participants were assessed every 4 weeks and received their last study treatment at Week 44. The study lasted 48 weeks, and 111 individuals were monitored until the end of the study

Week 48 (end of study)

At the end of the study, 93 participants entered a long-term study to receive **spesolimab** for up to 5 years

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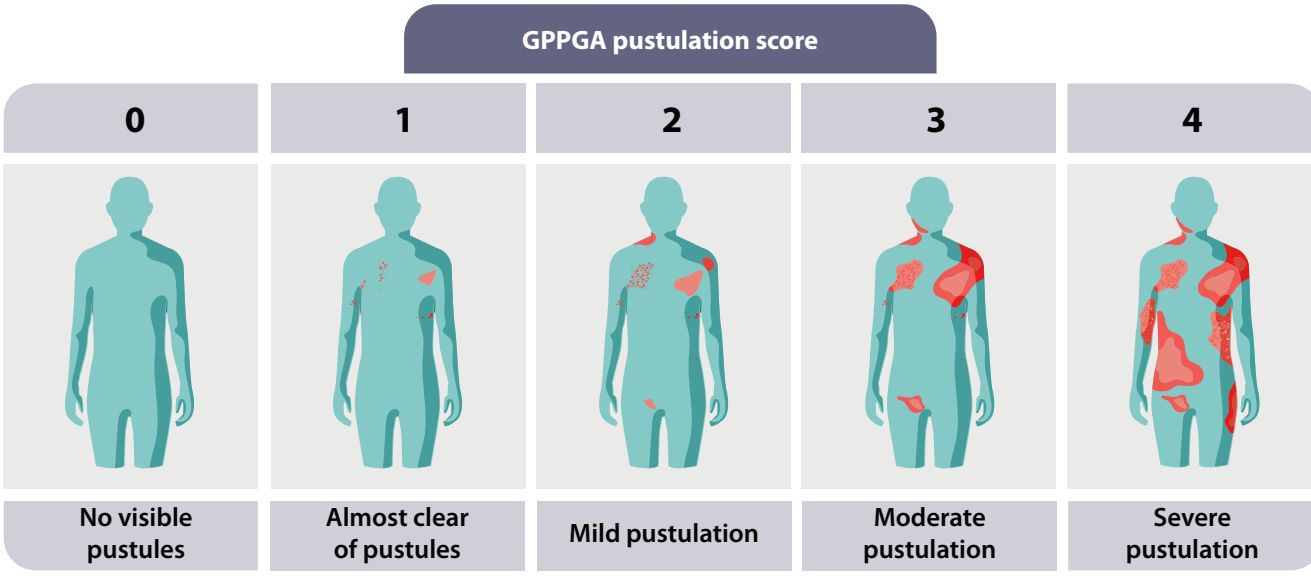
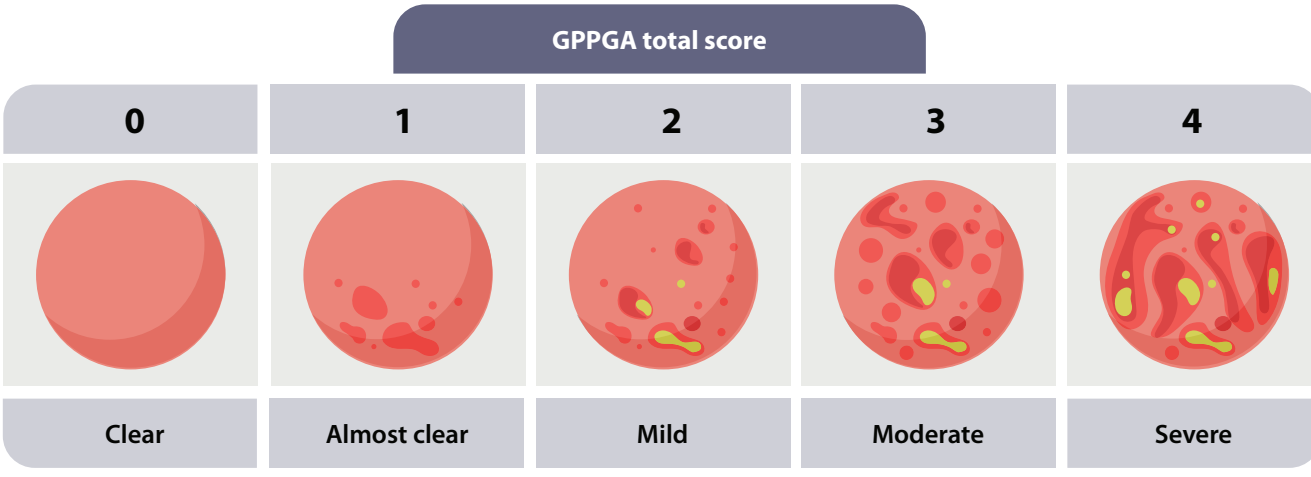
What did the study investigate?

The main aim of this study was to find out if **spesolimab** prevented GPP flares based on the strength of the drug dose that participants received. If the effects of a drug change when the dose of the drug is altered, for example, if it works better at a higher dose, the effects are said to be dose-dependent.

Loading dose: A higher dose of a drug that may be given at the beginning of a course of treatment before dropping down to a lower dose for the rest of the treatment period.

- The effects of three different doses of **spesolimab** (low, medium, and high) were compared to the effects of placebo in participants over 48 weeks. All treatments were given subcutaneously, meaning injected under the skin.
- The low dose consisted of an initial injection (termed **loading dose**) of 300 mg **spesolimab**, followed by 150 mg injections of **spesolimab** every 12 weeks. The medium dose was a 600 mg loading dose of the drug followed by 300 mg injections every 12 weeks, and the high dose consisted of a 600 mg loading dose followed by 300 mg injections every 4 weeks.
- The severity of a flare was evaluated using the Generalized Pustular Psoriasis Physician Global Assessment (shortened to GPPGA) pustulation subscore and GPPGA total score. Scores are given on a scale of 0 to 4 based on the redness, pustule density, crusting, and scaling of a participant's skin.
- A GPP flare was defined as a GPPGA pustulation subscore of 2 or more, and an increase in the GPPGA total score of 2 or more. GPP flares were also defined as worsening of disease (based on clinician's judgment) and/or if participants received specific medications for GPP.





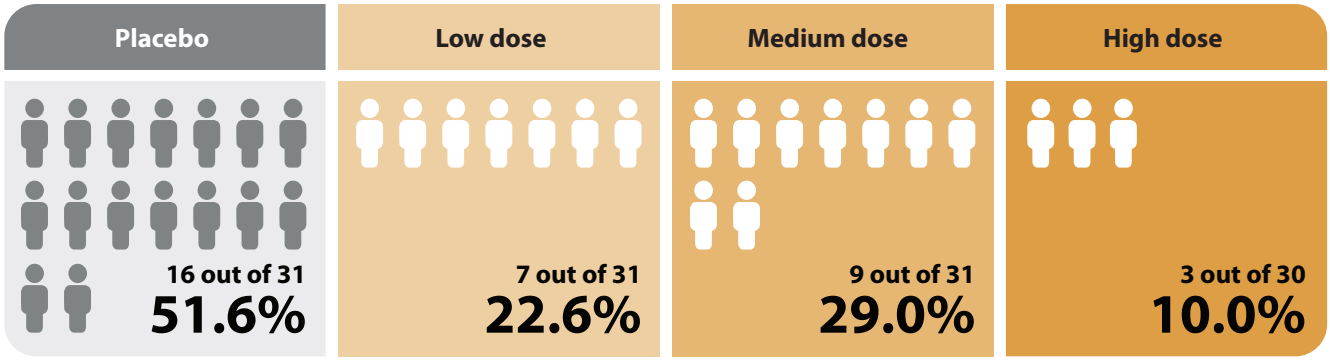
10.2217/frd-2023-0023

- The number of flares and the time at which they occurred were recorded for each participant over the 48-week study.
- Researchers also recorded which participants received any additional doses of **spesolimab** (given by injection into a vein) to treat flares during the study.
- Another aim of the study was to find out if **spesolimab** prevented worsening of a participant's quality of life.
- Information was also collected on how safe **spesolimab** was and if any **unwanted effects** were reported by participants.
  - All unwanted effects, such as illnesses or other health issues, were recorded. It is important to note that unwanted effects are not necessarily due to **spesolimab** and may be symptoms of GPP or caused by other medical problems.
  - Comparing unwanted effects with **spesolimab** to those that occurred in the placebo group helps understand how many of these issues can happen even when no drug is being taken.
  - This was carried out by asking participants to fill out two different questionnaires every 4 weeks. The first questionnaire asked them to rate their current symptoms, signs, and level of discomfort (Symptom score). The second questionnaire measured the overall effect of GPP on their lives (Quality of life score).
  - Disease worsening was defined as an increase of 4 points from the start of the study, for each scale.

Unwanted effects: Any untoward medical occurrence associated with the use of a drug in humans that may or may not be considered drug related.

What were the overall results of the study?

How many participants experienced flares?



- Of the three different doses of **spesolimab**, the high dose was the most effective, and reduced the chance of participants experiencing a flare by 84% compared with placebo

Percentage reduction in the chance of experiencing a flare in the high dose group **84%**

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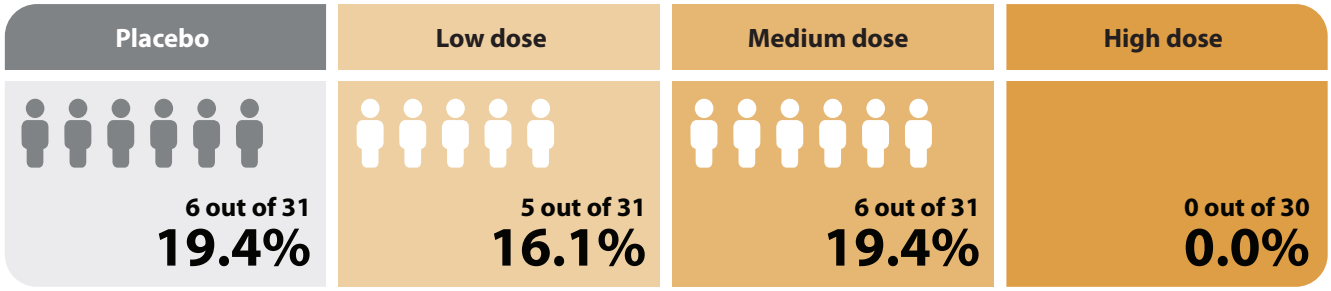
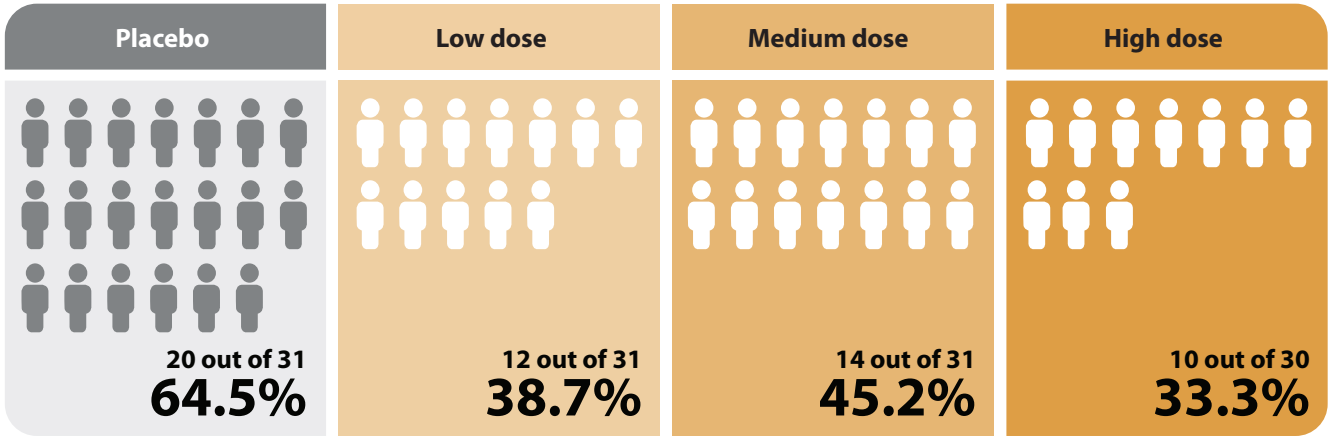
How many patients in each group experienced flares after Week 4?

- Participants who received high-dose **spesolimab** did not have flares after Week 4



How many participants experienced worsening of their quality of life?

- By the end of the study, a smaller proportion of participants in the low (12/31, 38.7%), medium (14/31, 45.2%), and high-dose (10/30, 33.3%) **spesolimab** groups reported a worsening of their symptom score compared with the placebo group (20/31, 64.5 %)



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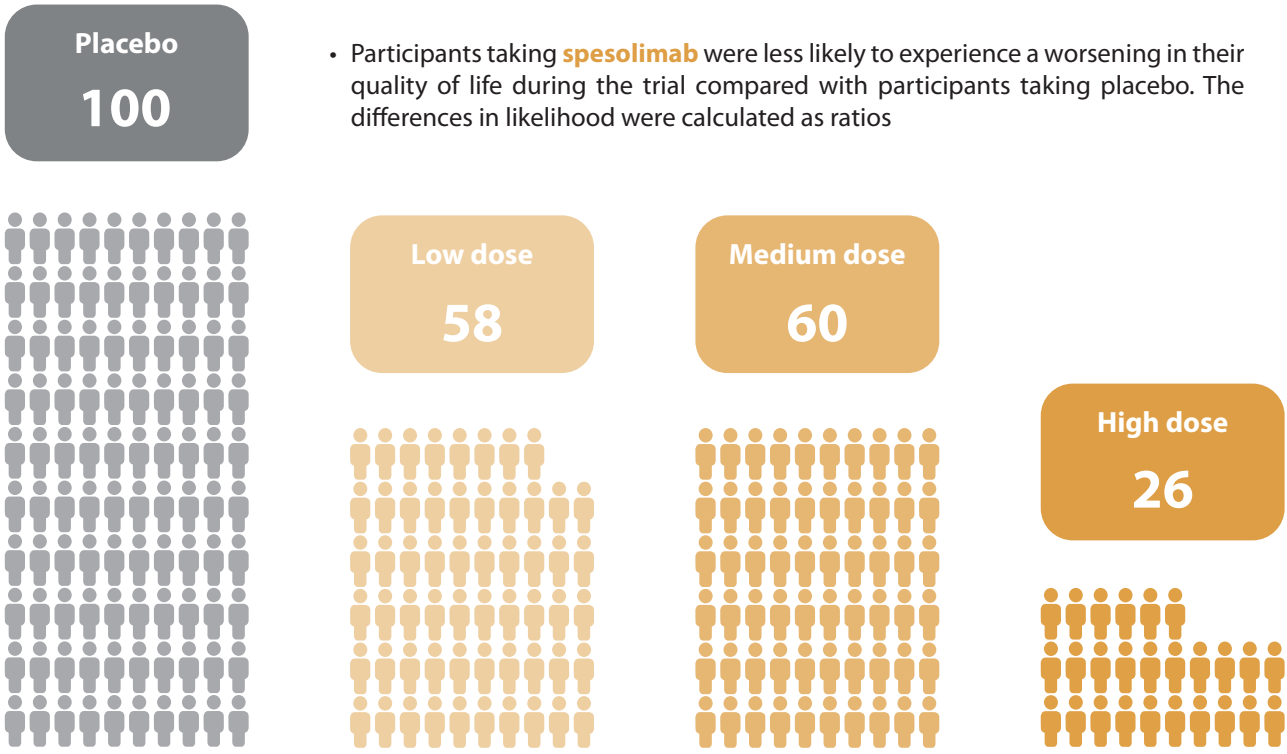
Spesolimab reduced the risk of a participant's quality of life score worsening over 48 weeks



- Participants taking **spesolimab** were less likely to experience a worsening in their quality of life during the trial compared with participants taking placebo. The differences in likelihood were calculated as ratios

- Using these ratios, we can estimate that if 100 participants receiving placebo had experienced a worsening in quality of life during the trial, only 58 receiving low dose **spesolimab**, 60 receiving medium dose **spesolimab**, and 26 receiving high dose **spesolimab** would have experienced a worsening in quality of life

How many participants experienced unwanted effects in this study?

- Overall, 90.3% (84 out of 93) of participants receiving **spesolimab**, and 86.7% (26 out of 30) of participants receiving placebo reported unwanted effects

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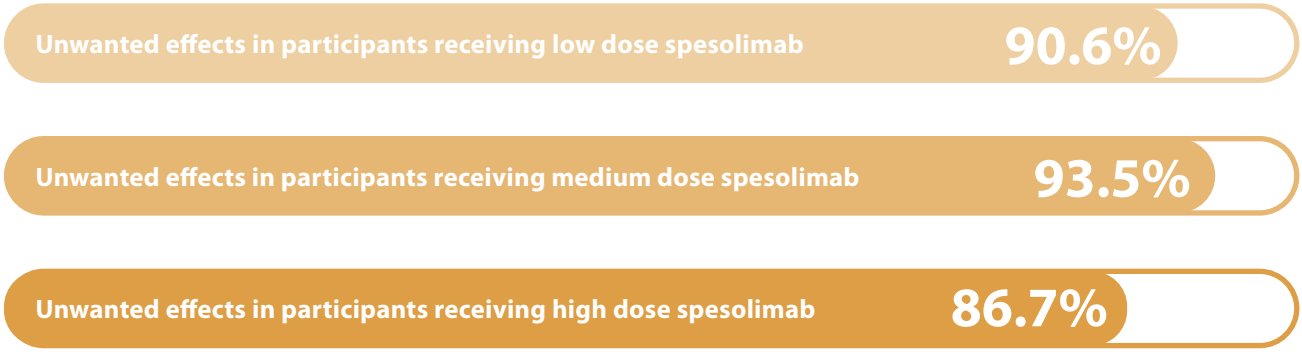
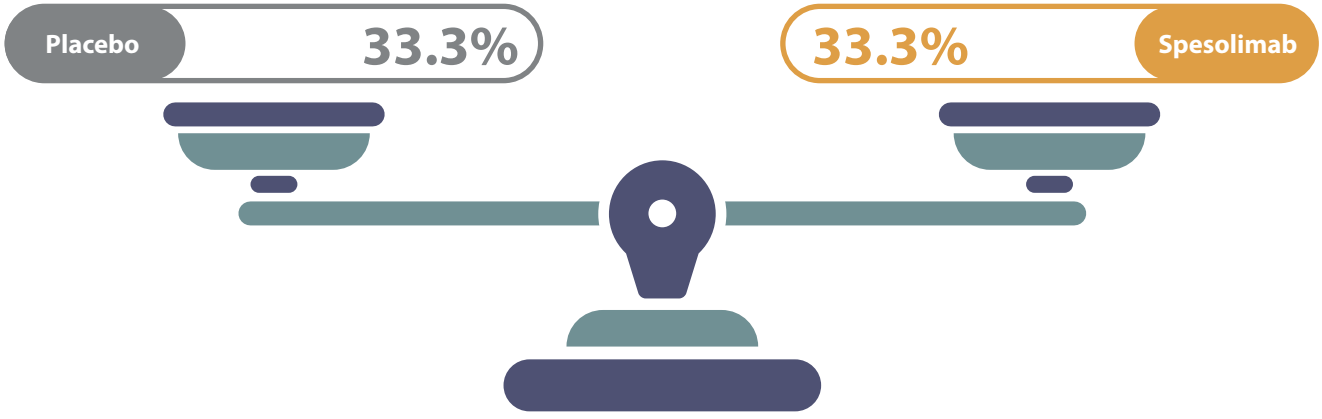
Were unwanted effects balanced between spesolimab groups?

- Unwanted effects occurred at a similar rate in participants who received low (90.6%, 29/32), medium (93.5%, 29/31), and high doses (86.7%, 26/30) of **spesolimab**

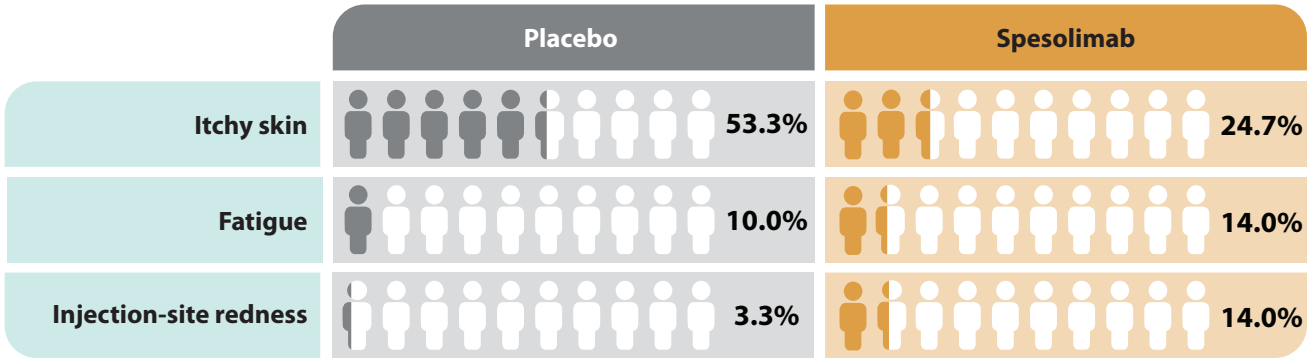


Was the rate of infections in participants balanced between study groups?

- Infections, including upper respiratory tract infections (such as the common cold) and COVID-19, were a common unwanted effect in people who received **spesolimab** (33.3%, 31 out of 93) and some events may be an effect of the drug. However, infections were equally as common in people who received placebo (33.3%, 10 out of 33)



Unwanted effects in patients receiving placebo and spesolimab



- The increased number of participants receiving **spesolimab** who experienced swelling, redness (erythema), pain, and itch at the injection site may be linked to the drug. However, this can be a common unwanted effect in studies where participants receive treatment by injections

Were there any serious unwanted effects in this study?

- Serious unwanted effects are any medical problem that leads to death, requires hospitalization, or causes disability. Such effects are not necessarily related to the treatment that participants receive during the study.
- A greater proportion of participants receiving **spesolimab** experienced serious unwanted effects (9.7%) compared with those receiving placebo (3.3%).
- Three serious unwanted effects (10%, 3 out of 30) were reported in participants who received a high dose of **spesolimab** including pustular psoriasis (worsening of GPP disease as defined by a clinician), breast cancer, and cholelithiasis (gallstones) (one participant each).
- There were no deaths in the study.

What do the results of the study mean?

- Participants treated with **spesolimab** had fewer flares than those in the placebo group.
- The results indicate that the high dose of **spesolimab** was the most effective at preventing flares.
- Long-term treatment with **spesolimab** also prevented the symptoms and quality of life of participants getting worse.
- The results are especially important because controlling long-term symptoms of GPP is a key goal for doctors and patients to manage the disease.
- The safety profile of **spesolimab** was favorable and there was no indication of increased rates of unwanted effects with a higher dose.
- These results indicate that **spesolimab** is an effective treatment for preventing flares in adolescents and adults with GPP.

Where can I find more information on this study?

The original article discussed in this summary, titled "Efficacy and safety of subcutaneous spesolimab for the prevention of generalized pustular psoriasis flares (Effisayil 2): a multicenter, randomized, placebo-controlled trial" was published in the *Lancet* in 2023. You can read the original article for a fee at:

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01378-8/fulltext

The full name of the study trial is "A Study to Test Whether Spesolimab Prevents Flare-ups in Patients With Generalized Pustular Psoriasis"

- You can read more about the study on the following websites:
  - Enter the study number NCT04399837 into the search field at: https://www.clinicaltrials.gov
  - Enter the EudraCT identifier 2018-003081-14 into the search field at: https://www.clinicaltrialsregister.eu/ctr-search/search
- You can read more about the 5-year open-label extension study of spesolimab by entering the study number NCT03886246 into the search field at: https://www.clinicaltrials.gov

A previously published PLSP containing additional background information on GPP and presenting the results of the Effisayil 1 study, in which the effects of spesolimab in treating GPP flares in patients were explored, can be found here:

https://doi.org/10.2217/frd-2022-0002

Educational resources

You can read more about GPP on the psoriasis.org website: www.psoriasis.org/pustular

Most countries have dedicated national psoriasis agencies and foundations. The websites of these agencies and foundations provide explanations, treatment options, educational resources, and support for people interested in psoriasis, and assistance in managing GPP following a diagnosis. Ask your healthcare provider or community support group to direct you to these websites.

Financial & competing interests disclosure

Full disclosure information for the authors can be found in the original article, found at this link:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01378-8/fulltext

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