

Future scientific research in CAD: Overview of the CASCADE trial

Eloy Roman, MD

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Disclaimer

- For educational purposes only
- Pegcetacoplan is an investigational therapy and has not been approved for the treatment of Cold Agglutinin Disease (CAD)
- This presentation is non-promotional and is sponsored by Sobi and Apellis

Disclosures

- I have received a speaker's fee from Swedish Orphan Biovitrum AB (Sobi) for this educational activity

What is Cold Agglutinin Disease (CAD)?

- A rare **autoimmune disease** in which the body's immune system mistakenly attacks and prematurely destroys its own **red blood cells (RBCs)**.¹ RBCs are responsible for carrying oxygen throughout the body. Destruction of RBCs results in the **inefficient delivery of oxygen to the body**²
- CAD primarily affects middle-aged and older adults and is reported in some studies to be more common among women than men¹
- CAD is more common among people living in colder climates³

Symptoms:¹

Symptoms are triggered by cold temperatures and may include:

- Fatigue
- Shortness of breath⁴
- Persistent blue or purple discoloration of the extremities (hands, feet, nose)
- Increased risk of blood clots⁵

There are two types of CAD:¹

- CAD **in the absence of** any underlying or associated disease such as an infection, another autoimmune disease, or certain cancers
- CAD **that is caused by** an underlying condition such as an infection, another autoimmune disease, or certain cancers

CAD: Cold agglutinin disease; RBC: Red blood cell.

1. NIH. Cold agglutinin disease 2021; 2. MD-health. Blood Health website 2022. Available at: <https://www.md-health.com/low-red-blood-cell-count.html>; 3. Berentsen S et al. Blood 2020; 4. Global Autoimmune Institute. Cold Agglutinin Disease (CAD); 5. Cold Agglutinin Disease News. Risk of Blood Clots Higher in CAD Patients Than General Population, Study Concludes. November 5, 2019.

What is the complement system and C3?

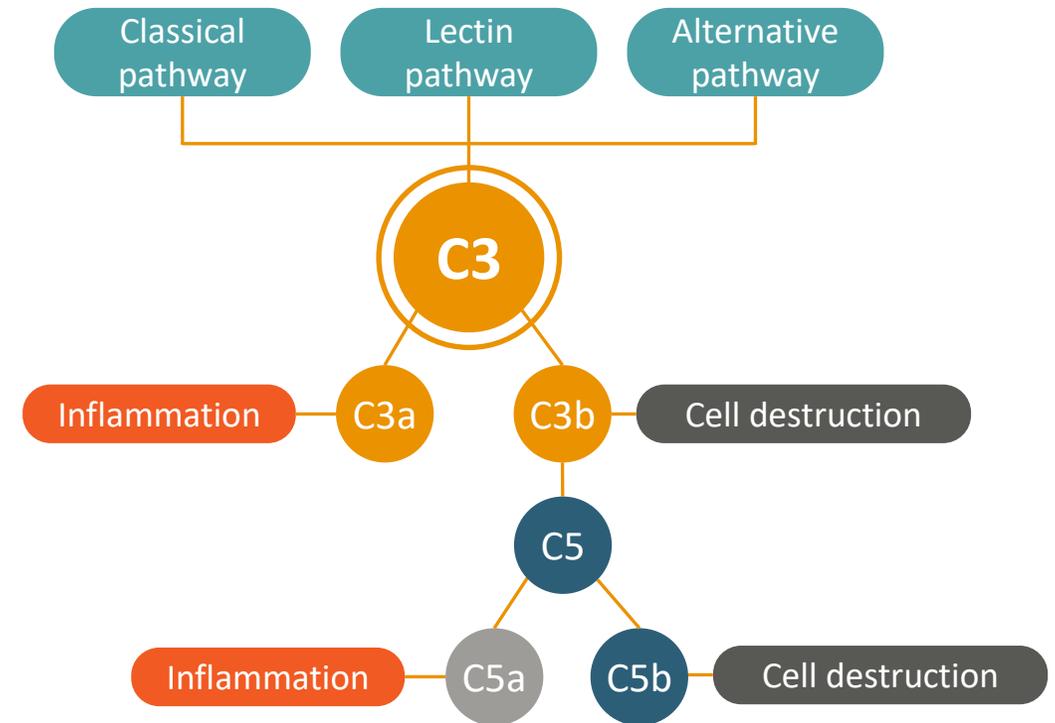
The complement system

The complement system is made of a series of proteins that are activated when the immune system is responding to a threat¹

C3: The central protein of the complement system

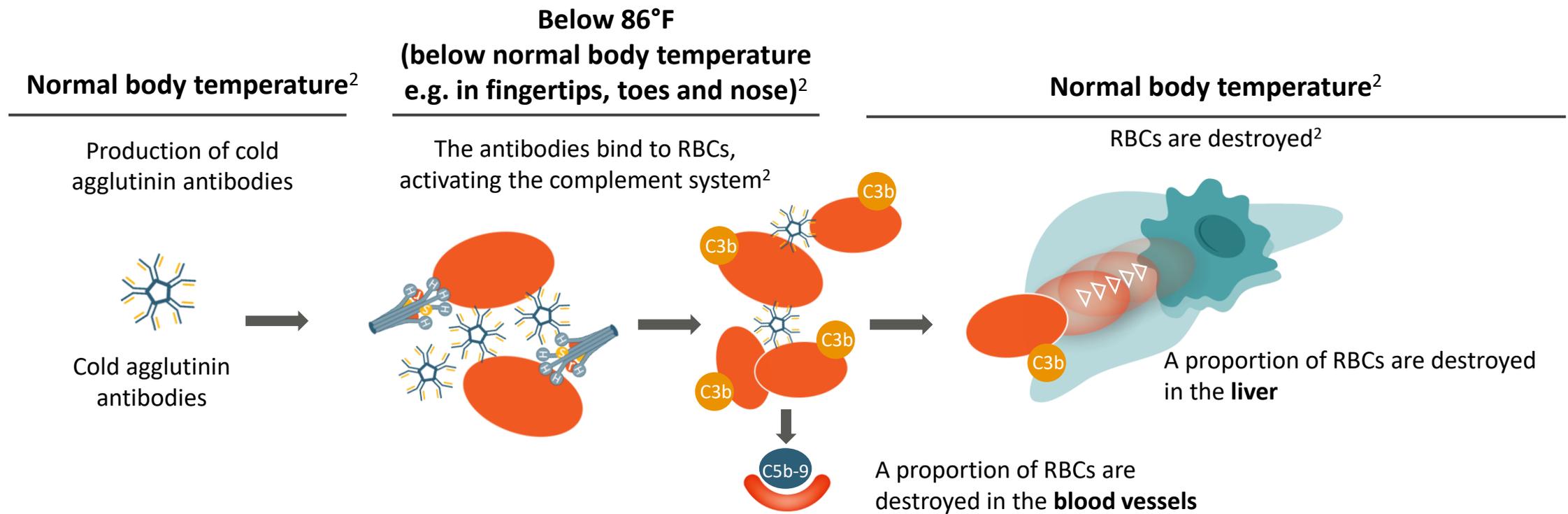
- All the activation pathways of the complement system converge at **C3**¹
- Centrally located, **C3** controls a comprehensive range of complement-driven immune effects including inflammation and cell destruction¹
- **C3b** causes cell destruction in the liver and spleen and **C5b** causes cell destruction in the blood vessels²

The complement system³



In CAD, the complement system is overactive¹

- In CAD, the immune system produces antibodies called cold agglutinins
- In cold temperatures, cold agglutinins bind to RBCs to trigger a series of reactions that lead to the destruction of RBCs (“**the complement system**”)



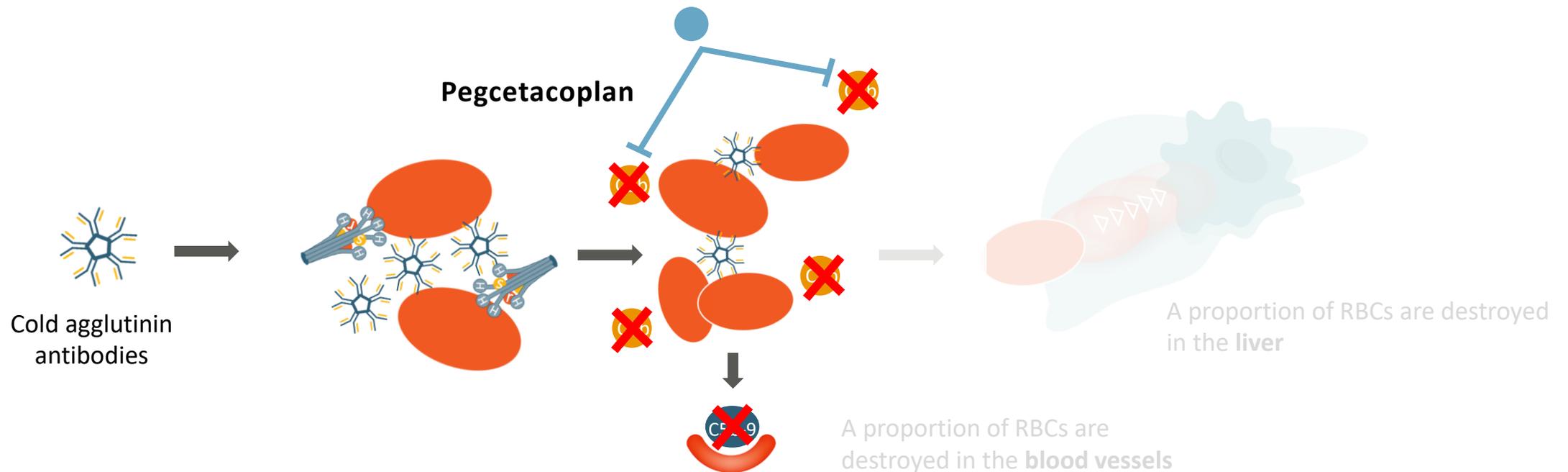
CAD: Cold agglutinin disease; C3: Complement component 3; C5: Complement component 5; RBC: Red blood cell.
1. Cold Agglutinin Disease News. The Complement System and Cold Agglutinin Disease 2021 ; 2. Adapted from Berentsen S. *Semin Hematol* 2018.

Aim of treatment in CAD: Reducing complement activity^{1,2}

Pegcetacoplan is an investigational therapy and has not been approved for the treatment of Cold Agglutinin Disease (CAD)

Pegcetacoplan aims to decrease the activity of the complement system by binding to C3 and C3b, which inhibits the production of key enzymes in the complement system

How pegcetacoplan aims to work in treating CAD²



CAD: Cold agglutinin disease; C3: Complement component 3; C5: Complement component 5; RBC: Red blood cell.

1. Cold Agglutinin Disease News. Apellis, Sobi Partner on Systemic Pegcetacoplan for CAD 2020; 2. Adapted from Berentsen S. *Semin Hematol* 2018.

CASCADE Study

A phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of pegcetacoplan in patients with CAD

What is a clinical trial and why are they important?



A **clinical trial** is any **research study** that prospectively assigns groups of patients to one or more treatment(s) to evaluate the **effects on health outcomes**¹

What do clinical trials measure?

Clinical trials **test whether a treatment** is:^{2,3}



Safe to use by monitoring for side-effects



Effective to use by comparing against other treatments or placebo (an inactive substance that looks like the treatment being tested)

Why are clinical trials important?

Clinical trials are key for **evidence-based medicine**, as testing the treatment on many people:³



Increases robustness of the results



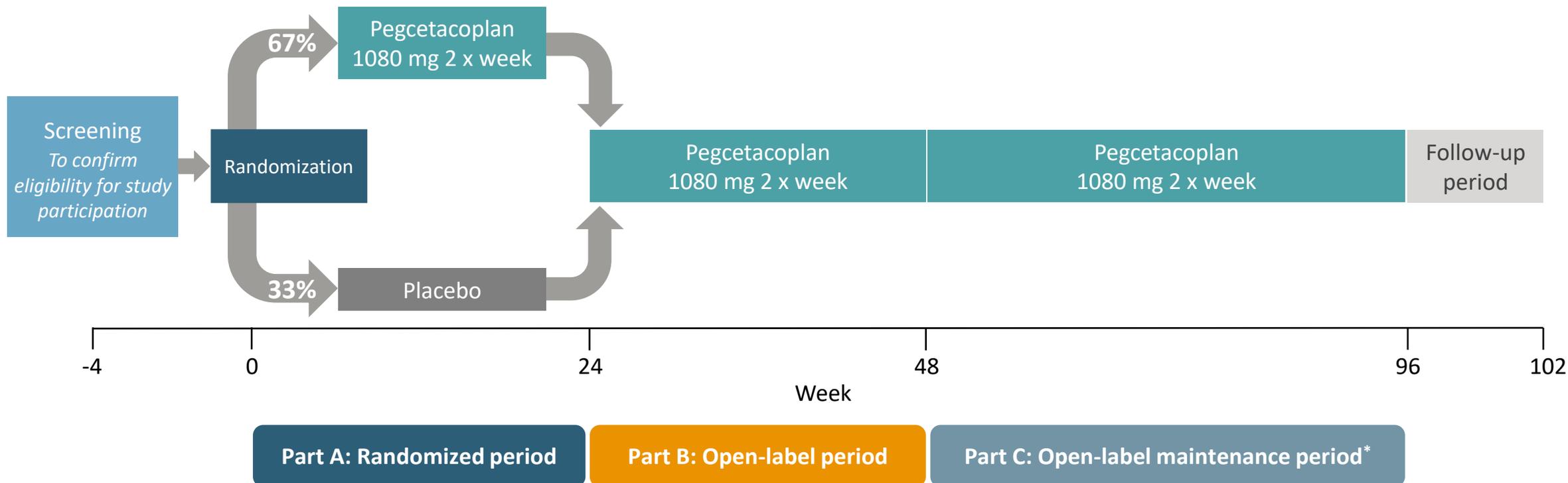
Provides an opportunity to **gain knowledge** on how to **better treat patients**

What does study participation involve?^{1,2}

Pegcetacoplan is an investigational therapy and has not been approved for the treatment of Cold Agglutinin Disease (CAD)



This clinical trial will assess the **safety** and **effectiveness** of **pegcetacoplan** in participants who have a **diagnosis of CAD** in the absence of any underlying or associated disease such as an infection, another autoimmune disease, or certain cancers³



CAD: Cold agglutinin disease.

*Open-label maintenance for a maximum of 48-weeks or until the product becomes commercially available.

1. ClinicalTrials.gov NCT05096403; 2. Sobi. PEGCET-101 CASCADE Participant information sheet; 3. NIH. Cold agglutinin disease.

What are the key measurements in the study?¹



Blood-related measurements

- Hemoglobin levels in blood
- Markers of RBC destruction in the blood
- Number of blood transfusions received



Life impact measurements

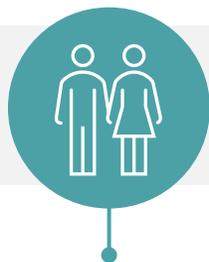
- Quality of Life (QoL) questionnaires
- Questionnaire on symptoms such as fatigue and shortness of breath



Safety and tolerability

- Monitoring for any side effects: laboratory testing, electrical activity of the heart and vital signs

Who participates in CASCADE? (1/2)¹



Be at least 18 years old



Diagnosis of CAD

In the absence of:²

- Any underlying or associated disease such as an infection
- Another autoimmune disease
- Certain cancers



**Hemoglobin levels of
9 grams per deciliter
(g/dL) or less**



For further information on the additional inclusion and exclusion criteria, please visit the link below:

<https://clinicaltrials.gov/ct2/show/NCT05096403>

Who participates in CASCADE? (2/2)¹

Pegcetacoplan is an investigational therapy and has not been approved for the treatment of Cold Agglutinin Disease (CAD)



Because pegcetacoplan is thought to reduce the activity of the complement system (a part of the immune system),² participants who have not received vaccines for diseases such as pneumonia and meningitis will need to have these before starting the study



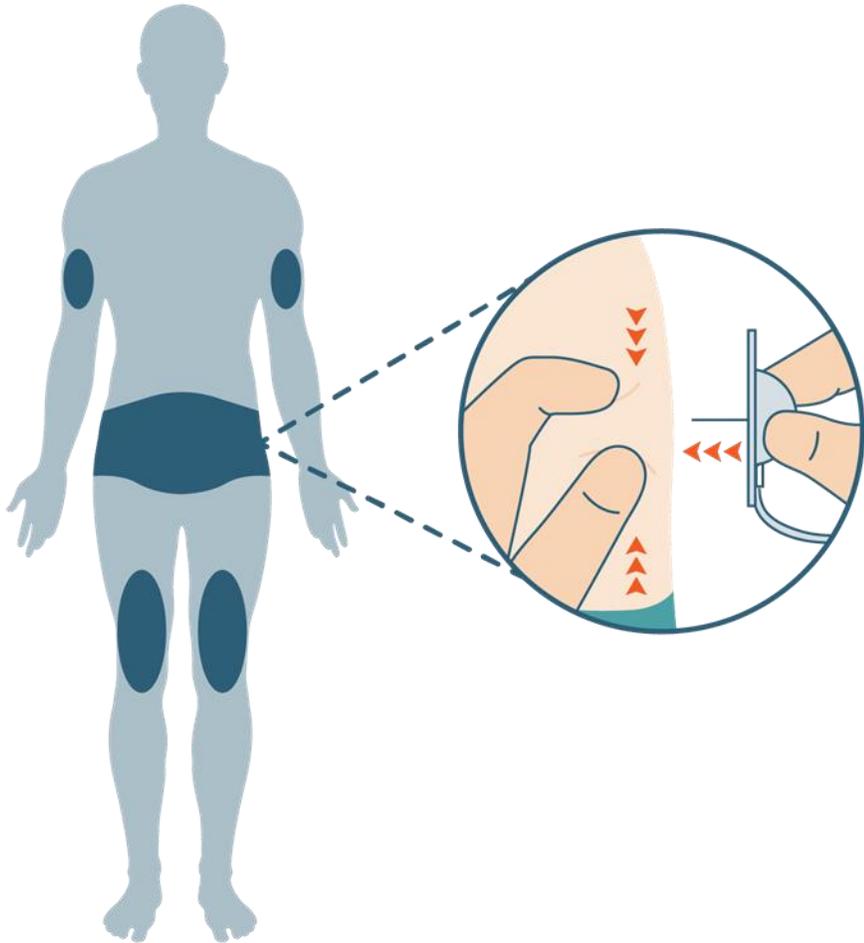
Participants that have recently received treatment with other anti-complement therapies or rituximab may require a period without treatment prior to the study



For further information on the additional inclusion and exclusion criteria, please visit the link below:
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How is the study drug generally administered?

Pegcetacoplan is an investigational therapy and has not been approved for the treatment of Cold Agglutinin Disease (CAD)



- The study drug (pegcetacoplan or placebo) is given as a subcutaneous infusion^{1,2}
- Two small needles are inserted into the fatty layer just below the skin (subcutaneously) and the drug slowly flows into the body (the process can take up to 60 mins)²
- Study participants and/or their caregivers will be trained to administer the study drug at home²
- Preferred site for infusion is the abdomen, but the thighs and upper arms can also be used²

Summary

Summary

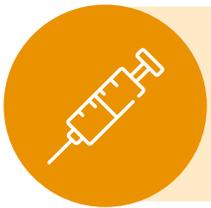
Pegcetacoplan is an investigational therapy and has not been approved for the treatment of Cold Agglutinin Disease (CAD)



CAD is a rare autoimmune disease in which the body destroys its own RBCs¹



C3 is the central protein of the complement system, which plays a key role in regulating inflammation and cell destruction²



Pegcetacoplan aims to reduce the activity of the complement system by binding to C3 and has been approved by the FDA for the treatment of another rare blood condition characterized by the destruction of RBCs³⁻⁵



The phase 3 CASCADE study is a multicenter, randomized controlled study that aims to assess the effectiveness and safety of pegcetacoplan in patients with CAD⁶

CAD: Cold agglutinin disease; C3: Complement component 3; FDA: Food and Drug Administration; RBC: Red blood cell.

1. NIH. Cold agglutinin disease 2016; 2. Merle NS et al. *Front Immunol* 2015; 3. Cold Agglutinin Disease News. Apellis, Sobi Partner on Systemic Pegcetacoplan for CAD 2020;

4. Cision PR Newswire. Aspaveli approved in EU as orphan drug for treatment of PNH 2021; 5. FDA. Empaveli (Pegcetacoplan) Prescribing Information 6. ClinicalTrials.gov NCT05096403.

CASCADE Study

If you are interested in finding out more information, please visit:
[**https://clinicaltrials.gov/ct2/show/NCT05096403**](https://clinicaltrials.gov/ct2/show/NCT05096403)

Or contact **Eloy Roman, MD**
Lakes Research, 5801 NW 151 Street,
Suite #302, Miami Lakes, FL 33014
[**eroman@lakesresearch.com**](mailto:eroman@lakesresearch.com)

Q&A

Thank you