Paroxysmal Nocturnal Hemoglobinuria (PNH) with Extravascular Hemolysis (EVH)

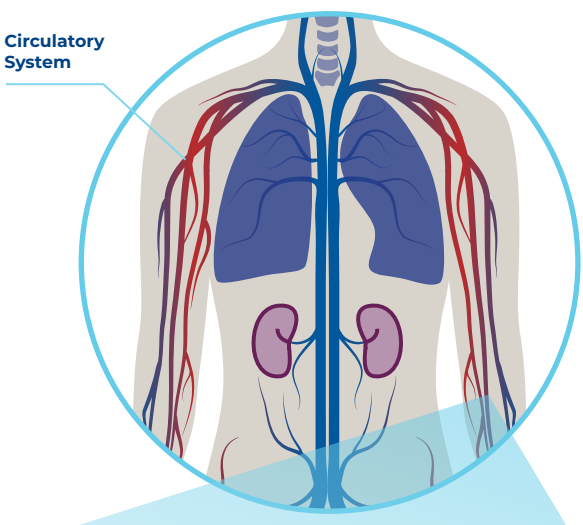
AstraZeneca Rare Disease

WHAT IS PNH?

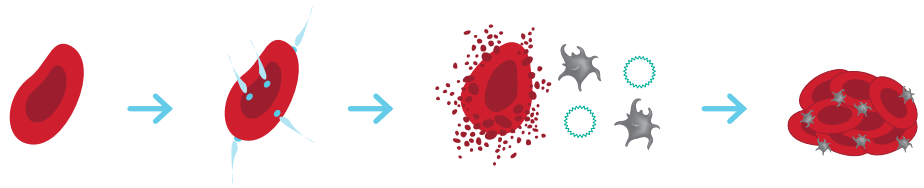
Paroxysmal nocturnal hemoglobinuria (PNH) **is a rare, chronic, progressive, and potentially life-threatening blood disorder.**

PNH is characterized by **red blood cell (RBC) destruction** within blood vessels (also known as **intravascular hemolysis,** or IVH) and **white blood cell and platelet activation**, which may lead to blood clots (thrombosis).

PNH is caused by an **acquired genetic mutation** (not inherited) that may happen any time after birth and results in the **production of abnormal blood cells** that are **missing important protective blood cell surface proteins**. These missing proteins enable the complement system to 'attack' and **destroy or activate these abnormal blood cells**.[1-3]

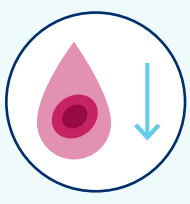


PNH Blood Cell Destruction Within the Blood Vessels



WHAT IS PNH WITH EVH?

Some people living with PNH who are treated with C5 inhibitors can continue to experience **anemia**. This can have various causes, including bone marrow failure or vitamin (folate) or hormone (erythropoietin) deficiencies, so it is important that all causes are explored. Sometimes, this continued anemia may be due to **extravascular hemolysis (EVH)**.[4]



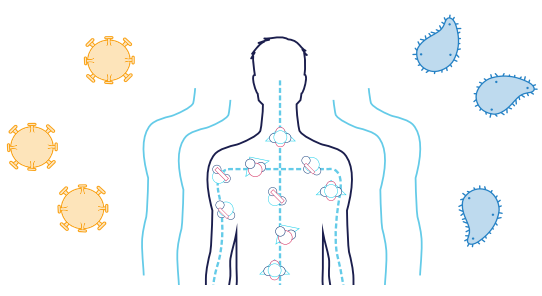
In EVH, **red blood cells are removed outside the blood vessels**. Since C5 inhibition enables PNH red blood cells to survive and circulate, EVH may occur when these now surviving PNH red blood cells are marked by proteins in the complement system for **removal by the spleen and liver**.[5]

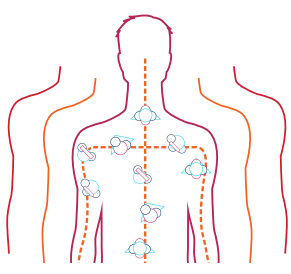
EVH may cause anemia and its related symptoms, such as fatigue, but importantly, it is **not life-threatening**.

For some people experiencing PNH with clinically significant EVH while on a C5 inhibitor, **blood transfusions may be required** to manage ongoing anemia-like symptoms.[6]

Once a person is treated with a C5 inhibitor for PNH, a physician may identify EVH using a blood test to **measure anemia** and by ruling out other causes of anemia, such as bone marrow disorders.[7]

THE COMPLEMENT SYSTEM





The complement system is a part of the immune system and is **essential to the body's defense against infection**.[8]

When the system is **thrown out of balance**, or dysregulated, these proteins can **trigger a dangerous, uncontrolled cascade of reactions** that attack cells and tissues resulting in **harmful inflammation** and the **destruction of healthy cells**.[9]

WHAT ROLE MAY COMPLEMENT INHIBITION PLAY IN TREATING PNH WITH EVH?

In PNH, **immediate, complete and sustained terminal complement inhibition** (by blocking the C5 protein) is the proven standard of care to **prevent the destruction of PNH red cells and activation of PNH white cells and platelets**. This helps reduce symptoms and complications and improve survival, transforming the lives of those impacted by PNH.

Alexion continues to **advance the understanding and treatment of PNH and PNH with EVH** as we explore new opportunities to target and inhibit key proteins in the complement cascade.

WHAT TREATMENT APPROACH IS BEING STUDIED BY ALEXION?

In addition to developing the **first approved therapy for PNH**, Alexion is currently pursuing an ongoing **Phase 3 clinical trial for people living with PNH who have clinically significant EVH while on a C5 inhibitor**. The study aims to investigate the safety and efficacy of blocking **Factor D**, another complement system protein, in combination with a C5 inhibitor.

Alexion has demonstrated an **unyielding commitment** to **unlocking the potential of the complement system** and continues to pioneer innovations in targeted complement inhibition and advance PNH research.

References:

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