**REVIEW**
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# Advancing Landscape of Paroxysmal Nocturnal Hemoglobinuria Treatment

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**Abstract**
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic bone marrow failure condition characterized by complement-mediated hemolytic anemia and thrombosis. Since its initial clinical description in 1882, somatic mutations in PIG-A were discovered in the 1990s. With an improved understanding of PNH biology, a focused effort on complement inhibitors led to the discovery of eculizumab, a C5 inhibitor initially approved by the FDA in 2007. Terminal complement pathway inhibition reduced intravascular hemolysis, anemia, and thrombosis. Further advancements in drug development for PNH include improved pharmacokinetics with ravulizumab in 2018 and the introduction of proximal complement inhibitors such as pegcetacoplan (2021), iptacopan (2023), and danicopan (2024), and crovalimab (2024) to enhance patient outcomes. With these new proximal and distal complement inhibitors in the treatment landscape, it is timely for clinicians to review the evolving landscape of PNH treatments and patient selection.
**Keywords:** Paroxysmal nocturnal hemoglobinuria; aplastic anemia; novel complement inhibitors

## Introduction

Paroxysmal nocturnal hemoglobinuria (PNH), described initially in 1882 by Paul Strübing, is a rare clonal hematopoietic stem cell disorder.(1) It is characterized by chronic hemolytic anemia due to complement-mediated red cell lysis, thrombosis, smooth muscle dystonia, and bone marrow failure (BMF).(2, 3) Until 2007, treatment for PNH was largely supportive, with stem cell transplantation being the only definitive therapy. The complement inhibitor eculizumab improved the prognosis for those with PNH by inhibiting C5-mediated intravascular hemolysis.(4) Eculizumab therapy greatly reduced mortality, improved quality of life, decreased fatigue and thrombotic risk, and reduced transfusion dependence and other anemia-associated symptoms.(4-6) However, a significant proportion of patients with PNH continue to experience breakthrough hemolysis and transfusion dependence due to C3-mediated extravascular hemolysis despite eculizumab therapy.(7-9) The development of novel complement inhibitors has changed the treatment paradigm for patients with PNH suffering from anemia owing to extravascular as well as breakthrough hemolysis. These novel agents and the evolving PNH treatment landscape are discussed in this review.

## Pathophysiology

Paroxysmal Nocturnal Hemoglobinuria arises from an acquired mutation in the *PIGA* gene, which plays a critical role in the biosynthesis of glycosylphosphatidylinositol (GPI) anchors.(10-12) These anchors are essential for attaching various surface proteins, including CD55 (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis), which regulate complement activation.(13, 14) *PIGA* mutated hematopoietic stem cells (HSCs) produce erythrocytes deficient in CD-55 and CD-59, leaving them vulnerable to complement-mediated lysis.(12) This loss of complement regulation underlies hemolysis in PNH.(11) *PIGA*-mutated cells may be present in low and clinically insignificant amounts. Evolution to PNH requires clonal expansion of the *PIGA*-mutated population and frequently occurs in the setting of aplastic anemia (AA). The mechanism of clonal expansion is believed to be due to a survival advantage of *PIGA*-mutated cells compared to the normal HSC population in the setting of AA.(15, 16) AA and PNH are closely related disorders

due to their shared immune-mediated pathogenesis. 40% of AA patients have detectable PNH clones, and 10-30% of all AA patients will eventually develop hemolytic PNH.(17) Because PNH is a bone marrow failure disorder linked to T-cell–mediated autoimmunity, it is also associated with an increased risk of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Approximately 2% to 6% of PNH patients develop secondary MDS/AML within 10 years. The prevalence is 9% in PNH patients with AA.(17) Factors associated with progression from PNH to secondary MDS/AML include longer duration of disease, increased telomere attrition, presence of adverse prognostic mutations, and multiple mutations.(17, 18) Thrombosis is the most common cause of morbidity and mortality in patients with PNH and is responsible for approximately 40% to 67% of deaths.(19) The mechanism of thrombosis in PNH has not been entirely elucidated but is attributed to a combination of factors.(20, 21) Notably, thrombosis in PNH is more common in patients with large PNH clones (>50% PNH granulocytes).(22) PNH is associated with both venous and arterial thrombosis, but venous sites are most common.(19) Thrombosis may occur in typical sites such as the limbs and lungs as well as in more unusual sites such as the sagittal and cavernous sinuses, mesenteric veins, and the hepatic vein (Budd-Chiari syndrome). Budd-Chiari syndrome is the most common thrombotic event in patients with PNH.(19, 20, 23)

**Management of PNH**

In general, therapy should be initiated in patients exhibiting symptoms of significant hemolysis, such as severe anemia, thrombosis, pain paroxysms, debilitating fatigue, and worsening renal insufficiency.(15, 16) The size of the PNH clonal population is another factor to consider in initiating treatment. Patients with small clonal population (usually <30%), often lack clinical hemolysis and PNH associated symptoms, and therefore do not benefit from complement inhibitors. In contrast, those with large a large PNH clonal population (usually >50%) do benefit from complement inhibitors. For symptomatic patients with a moderate PNH clonal population (30-50%), treatment should be based on symptom severity. Providers should assess each case individually, as some patients may still benefit from complement inhibitor therapy.(24)

The goals of PNH treatment are to limit complement-mediated hemolysis, subsequent complications and ultimately improve survival patient survival. The efficacy of PNH treatment can be measured by several key endpoints. The degree of hemolysis is estimated using lactate dehydrogenase (LDH) levels, reticulocyte counts, and hemoglobin levels. Other disease- and treatment-related endpoints include thrombotic events, breakthrough hemolysis, fatigue (as measured by Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue] scale), and transfusion dependency. To understand the need for novel therapeutics and their clinical application, we discuss the following types of hemolysis seen in PNH: (i) breakthrough hemolysis and (ii) extravascular hemolysis, along with its differences from intravascular hemolysis.

**Breakthrough hemolysis**

Two humanized monoclonal antibodies (mAbs), eculizumab and ravulizumab, target C5 and are approved by the Food and Drug Administration (FDA) for use in patients with PNH. Breakthrough hemolysis (BTH) usually occurs while a patient is on complement inhibitor therapy. BTH can be attributed to suboptimal C5 inhibition and may be pharmacokinetic (i.e. suboptimal C5 inhibition/dosing or missed treatments). Serum drug trough levels may become too low, particularly with eculizumab in last few days of each biweekly cycle. Pharmacodynamic BTH is likely due to conditions that lead to complement activation, such as infections. When the C3b density on the erythrocyte surface is too high, high-affinity C5 convertases can cleave C5 even when bound to a C5 inhibitor or cause conformational changes to C5 triggering hemolysis.(7-9)

**Extravascular hemolysis**

While C5 inhibitor therapy can effectively halt complement-mediated intravascular hemolysis in patients with PNH, anemia tends to persist in a subset of patients due to extravascular hemolysis (EVH).(15, 25) The PNH erythrocytes of patients on therapy accumulate C3 fragments, particularly C3d, on their surface, which then serve as opsonins. Opsonized erythrocytes are subsequently recognized and phagocytosed by macrophages. Consequently, EVH occurring in the liver and spleen leads to anemia.(15, 25) This can be identified by a persistently high reticulocyte count with concomitant anemia. Notably, C3 fragments are detected only on PNH erythrocytes after C5 inhibitor treatment. This can be identified using flow cytometry and/or a Coombs test. Normal erythrocytes are not coated by C3 fragments, even after C5 inhibitor treatment. This is likely due to the deficiency of CD55 in PNH cells, as CD55 is a regulator of the C3 convertase. As C5 inhibitors block the complement pathway at the level of C5, the earlier steps in the pathway continue to occur. The activation, deposition, and proteolytic cleavage of C3 to C3b result in the accumulation of C3 fragments on the surface of PNH erythrocytes creating the conditions necessary for significant EVH.(25) Recognition of this limitation in PNH therapy prompted the development of C3 inhibition therapies aimed at preventing both intravascular and extravascular hemolysis. The blockade of C3 abolishes intravascular hemolysis by directly inhibiting C3 and prevents EVH by stopping the accumulation of C3d on the surface of PNH erythrocytes.(7)

**Current approved PNH therapeutics**

**Eculizumab**

The first line treatment of PNH has historically been eculizumab, an anti-C5 mAb first approved by the FDA in 2007.(26) Eculizumab compensates for the lack for CD59 by binding C5 and preventing its cleavage by the C5 convertase (Figure). Inhibiting C5 cleavage prevents the formation of the MAC and limits intravascular hemolysis. However, eculizumab does not compensate for the lack of CD55. As a result, the deposition of C3b opsonin will continue, and mild to moderate extravascular hemolysis in the liver and spleen may still occur.(22) Eculizumab significantly reduces hemolysis, as demonstrated by marked declines in LDH in all patients to near normal levels after 1 week.(5) FACIT-Fatigue showed a mean 12.2 point improvement during the course of the trial (scored 0-52, higher scores indicate improvement).(5) Additionally, 51% of participants remained transfusion independent during the course of the trial. The average number of RBC units required by participants dropped from 12.3 units per patient in the preceding year to 5.9 during the eculizumab trial.(5)
During the trial, two patients experienced a thrombotic event (one DVT and one PE). The most common side effect reported was headache (96.4%). Headache is likely associated with acute increase in NO levels shortly after beginning eculizumab. Headache is rarely reported after the first few doses.(5) Reduction of thrombotic events results in dramatically improved survival in patient receiving eculizumab therapy. A follow up retrospective study examined a PNH cohort taking eculizumab between 2002 and 2010. The 5-year survival rate on eculizumab was 95.5%, with no treatment-related deaths, compared to 66.8% in the pre-eculizumab control group. Before initiating eculizumab, there were 34 thrombotic events in 21 of the patients. After eculizumab, there were only 2 thrombotic events. The rate of thrombosis decreased from 5.6 to 0.8 thrombotic events per 100 patient years on eculizumab.(27) Furthermore, 21 patients who were previously on prophylactic anticoagulation were able to discontinue therapy without experiencing any thrombotic events after cessation.(27)

**Ravulizumab**

The next advancement in C5 inhibition occurred in 2018 with the approval of Ravulizumab, a mAb C5 inhibitor with a higher binding affinity for C5 than eculizumab (Figure).(28) Ravulizumab requires dosing every eight-weeks, whereas eculizumab requires biweekly administration (Table 1).(28) This extended dosing interval is achieved through enhanced endosomal recycling of the mAb. The Ravulizumab 301 Phase 3 trial compared ravulizumab and eculizumab in complement-inhibitor-naïve patients with PNH. Ravulizumab demonstrated non-inferiority in both primary endpoints: transfusion avoidance and hemolysis, measured by LDH. Among patient receiving ravulizumab, 73.6% avoided transfusion compared to 66.1% in the eculizumab group.(29) LDH normalization was observed in 53.6% of patients on ravulizumab patients compared to 49.4% on Eculizumab. Breakthrough hemolysis occurred at lower rates in the ravulizumab group (4.0%) compared to the eculizumab group (10.7%).(29) The ravulizumab 302 Phase 3 trial evaluated the efficacy of ravulizumab versus eculizumab in patients previously treated with eculizumab. Ravulizumab demonstrated non-inferiority in the primary endpoint: change from LDH baseline. The ravulizumab group demonstrated a 0.82% reduction in LDH from baseline while the eculizumab group showed an 8.39% increase from baseline.(30) No patients in the ravulizumab group experienced breakthrough hemolysis, whereas 5 patients (5.1%) in the eculizumab group did. The mean number of RBC units transfused was comparable between the groups, with ravulizumab patient receiving an average of 4.3 units.(30) The FACIT-fatigue scores were also comparable between the groups, with ravulizumab demonstrating a 2.01-point improvement from baseline and eculizumab showing a 0.54-point improvement.(30) No patients in either group experienced a major adverse vascular event (MAVE). Headache was the most frequently reported adverse event occurring in 26.8% of the ravulizumab group and 17.3% of the eculizumab group.(29, 30)

**Pegcetacoplan**

Pegcetacoplan, a peptide-based inhibitor of C3 designed to control both intravascular and extravascular hemolysis, received FDA approval in 2021 for treatment of PNH (Figure).(31) A Phase 3 trial evaluated the efficacy and safety of pegcetacoplan monotherapy versus eculizumab in patients with PNH with hemolysis poorly controlled by eculizumab (hemoglobin <10.5g/dL). Pegcetacoplan demonstrated superiority to eculizumab in limiting hemolysis. The mean hemoglobin change from baseline in the pegcetacoplan group was an increase of 2.37 g/dL, whereas the eculizumab group experienced a mean decreased of 1.47 g/dL (Table 2). The mean hemoglobin difference between treatments was 2.69 g/dL in favor of pegcetacoplan.(32) A total of 85% of patients in the pegcetacoplan group avoided transfusion, compared to only 15% in the eculizumab group.(32) FACIT-Fatigue scores increased by an average of 9.2 points in the pegcetacoplan group and decreased by 2.7 points in the eculizumab group.(32) BTH occurred in 10% of patients receiving pegcetacoplan and 23% of those receiving eculizumab.(32) The most common adverse event in both groups was infusion site reaction. Headache was reported in 7% of those taking pegcetacoplan, compared to 23% in the eculizumab group.(32)

**Iptacopan**

Iptacopan was approved in 2023 as the first oral monotherapy for treatment of PNH in adults (Table 1).(33) Iptacopan is a selective inhibitor of Factor B. Inhibiting Factor B prevents the formation of the C3 convertase, thereby limiting complement pathway amplification and significantly reducing hemolysis (Figure). Adding iptacopan led to significant reduction in LDH levels, from 539 IU/L at baseline to 235 IU/L at week 13(34).

Significant improvements were observed in other hematological markers, and no serious adverse events were reported.(34) A follow up 12-week Phase 2 trial evaluated iptacopan monotherapy in patient with PNH who had not received complement inhibition therapy in the previous three months and had an baseline hemoglobin level of 8.58 g/dL.(35) At week 12, LDH levels decreased by ≥60% from baseline. Hemoglobin levels improved from 8.85 to 11.52 g/dL in Cohort 1 and from 7.69 to 10.9 g/dL in Cohort 2 (Table 2).(35) Five patients achieved hemoglobin levels >12.0 g/dL and an overall upward trend persisted beyond the 12-week period.(35) All but one patient remained transfusion independent during the trial. The patient requiring transfusion had preexisting MDS and was enrolled despite significant reticulocytopenia. No serious adverse events were reported. The most commonly reported adverse event was headache, affecting 4 out of 13 participants.(35)

**Danicopan**

Danicopan is an oral, small-molecule inhibitor of Factor D approved for PNH treatment in 2024.(36) Factor D is a serine protease that catalyzes the cleavage of Factor B into its active components. Inhibiting Factor D prevents the formation of an active C3 convertase, thereby blocking amplification of the complement pathway (Figure). Factor D is an attractive drug target because it catalyzes a rate-limiting step in complement amplification and is present at the lowest concentration of any complement protein.(37) In the Phase 3 ALPHA clinical trial, danicopan was evaluated as an add-on treatment in patients with clinically significant extravascular hemolysis (EVH) despite treatment with a C-5 inhibitor. A total of 42 participants received danicopan 150 mg three times daily, while the placebo group continued to receive eculizumab or ravulizumab monotherapy. Danicopan treatment resulted in a clinically significant increase in mean hemoglobin concentration of 2.94 g/dL after 12 weeks (Table 2).(38) Danicopan in combination with ravulizumab or eculizumab achieved a >2g/dL increase in hemoglobin in 60% of patients and achieved transfusion avoidance in 83% of patients.(38) The placebo group demonstrated a 0.5 g/dL increase in Hgb and no members of the placebo group exhibited an increase of Hgb concentration >2.0 g/dL.(38) FACIT-Fatigue improved by a mean of 8 points in the danicopan group at 12 weeks, compared to 2.6 points in the placebo group.(38) No thromboembolic or other significant adverse events were reported. These findings suggest that danicopan is a promising therapeutic option for patients who continue to have clinically significant EVH despite C5 inhibitor therapy.

**Crovalimab**

Crovalimab, a humanized, anti-complement component C5 (anti-C5) monoclonal antibody, is the latest development in PNH treatment, and was approved in June 2024 in adult and pediatric patients 13 years and older with a body weight of at least 40 kg. This approval was based on data from COMMODORE 2 (Table 1).(39) There were 2 primary end points: hemolysis control from week 5 to week 25 and transfusion avoidance from baseline to week 25. Key secondary end points included breakthrough hemolysis from baseline to week 25, stabilized hemoglobin from baseline to week 25, and mean change in fatigue in adult patients from baseline to week 25. Data showed that crovalimab was noninferior to eculizumab in respect to breakthrough hemolysis rates (10.4% vs 14.5%) and hemoglobin stabilization (63.4% vs 60.9%)(Table 2).(40) The advantage of crovalimab is its once-monthly subcutaneous administration.(41) The rates of any-grade treatment-related adverse effects (AEs) were 33.3% for crovalimab vs 34.8% for eculizumab. The rates of grade 3 to 5 AEs were 17.8% and 24.6%, respectively.(40)

**Place of Allogeneic hematopoietic stem cell transplantation**

While complement inhibitors remain the standard of care for patients with paroxysmal nocturnal hemoglobinuria (PNH) experiencing hemolysis, allogeneic hematopoietic stem cell transplantation (HSCT) may be considered as an alternative for those with refractory disease or severe adverse effects from non-transplant therapies. According to the International Bone Marrow Transplant Registry, the 2-year overall survival (OS) rate was 56% among 48 recipients of HLA-identical sibling transplants performed between 1978 and 1995.(42) A more recent retrospective study evaluated 240 PNH patients who underwent HSCT between 2011 and 2020 across 125 EBMT transplant centers in the Netherlands, reporting a 3-year OS rate of 79%, with infections and graft-versus-host disease (GVHD) identified as the primary causes of mortality.(43) Survival was associated with both donor type and patient age: 3-year OS rates were 86% for HLA-matched sibling donors, 78% for matched unrelated donors, and 62% for mismatched unrelated donors (p=0.003).(43) Age-stratified OS rates were 83% for patients <20 years, 82% for those aged 20–40 years, and 67% for patients >40 years.(43) Although outcomes following HSCT have improved over the past decade—due to advances in donor selection, conditioning regimens, GVHD management, and post-transplant care—HSCT should be reserved for cases where other treatment options are contraindicated or have failed, owing to the persistent risks of infection and graft failure.

**Gene therapy and other biologics**

Gene therapy to restore PIGA function or block the complement pathway has long been explored as a potential treatment for PNH. In vivo studies have demonstrated that lentiviral vectors can effectively deliver a functional copy of the *PIGA* gene to hematopoietic stem cells (HSCs), thereby re-establishing the expression of glycosylphosphatidylinositol-anchored proteins (GPI-APs).(44) HMI-104, an adeno-associated virus (AAV)-based gene therapy, has shown success in utilizing hepatic expression of a C5 monoclonal antibody (C5 mAb),

resulting in complete inhibition of ex vivo hemolysis.(45) Human studies have yet to be performed, but single time therapy and a potential lifetime cure makes such an approach attractive for PNH patients.
Another agent, KP104, is a bifunctional fusion protein that combines an anti-C5 monoclonal antibody with the regulatory domains of complement factor H allowing inhibition of the terminal and proximal complement pathway simultaneously. Phase 2 trial (N=18) results have demonstrated that in all patients KP104 therapy induces rapid and sustained increases in hemoglobin levels, significant reductions in lactate dehydrogenase, and a complete elimination of transfusion requirements in treated patients.(46)

**Patient selection and choice of therapy**

Shared decision-making plays a vital role in selecting the most appropriate treatment for PNH. PNH management has advanced significantly as the PNH clinician community has widely adopted eculizumab and largely transitioned to ravulizumab due to its more convenient dosing schedule. Now with subcutaneous injections and oral agents available, PNH management has become increasingly nuanced. While many clinicians await long-term safety data on proximal complement inhibitors, a well-validated quality-of-life tool is needed to determine whether additional proximal inhibition is necessary for patients on C5 inhibitors who do not have severe anemia. At the same time, key considerations when selecting a treatment include the patient's preference for route of administration, the clinician's assessment of adherence to oral or subcutaneous therapy, and the management strategy for complement activation episodes.

**Remaining Challenges in PNH**

With ongoing advances in treatment options, PNH is significantly more manageable today compared to the pre-eculizumab era. However, several challenges remain:

1. Underdiagnosis of PNH remains prevalent due to its rarity.
2. Hematopoietic stem cell transplantation remains the only curative therapy,and 2% to 6% of patients with PNH develop clonal evolution to myelodysplastic syndrome or acute myeloid leukemia.(17)
3. Reliable predictive tools to identify clonal evolution do not exist.
4. Assessing residual anemia in patients with PNH is a challenge. The relative contributions of bone marrow failure, clonal evolution, and EVH must be carefully evaluated.
5. Breakthrough hemolysis remains a concern with novel agents despite its low incidence in trials.
6. Managing hospitalized patients with PNH on oral therapy may be challenging, as most of these medications are non-formulary in U.S. hospitals.
7. The high cost of the novel oral agents remains a significant barrier to widespread adoption in the community. Due the expense proximal complement inhibitors, C5 inhibitors continue to be the first line therapy in most institutions, with gradual paradigm shift towards oral agents. Most physicians select a therapy based on extensive discussion with individual patients about their preferences. Long-term safety and real-world evidence will facilitate a shift in the standard of care toward more convenient oral agents.

**Conclusion:**

PNH is a rare clonal hematopoietic stem cell disorder characterized by chronic hemolytic anemia, thrombosis, smooth muscle dystonia, and bone marrow failure. Stem cell transplantation remains the only curative therapy. Over the years, novel complement inhibitors have been developed to improve survival and quality of life, making PNH a more manageable disease. The emergence of multiple novel therapies has made shared-decision making essential, requiring a thorough evaluation of all available treatment option in collaboration with the patient.

**Disclosures:**

Swapna Thota MD: Advisory role: Novartis, Daichii Sankyo, Alexion, Sobi Inc, Pharmaessentia Inc, AAMDS Foundation

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**Table 1: FDA approved treatments for PNH: approval year, mechanism of action, and dosing**

| Drug (Brand Name) | Approval Year | Mechanism of Action | Loading Dose | Maintenance Dose | Route | Dosing Frequency |
|---|---|---|---|---|---|---|
| Eculizumab (Soliris) | 2007 | C5 inhibitor | 600 mg IV weekly × 4 weeks | 900 mg | IV | Q2W |
| Ravulizumab (Ultomiris) | 2018 | C5 inhibitor | Weight-based IV dose (2400–3000 mg) | 3000–3600 mg | IV | Q8W |
| Pegcetacoplan (Empaveli) | 2021 | C3 inhibitor | None | 1,080 mg | SUBQ | BIW |
| Iptacopan (Fabhalta) | 2023 | Factor B inhibitor | None | 200 mg | Oral | BID |
| Danicopan (Voydeya) | 2024 | Factor D inhibitor | None | 150 mg | Oral | TID |
| Crovalimab (Piasky) | 2024 | C5 inhibitor | 1,000 mg IV on Day 1, then 4 weekly 340 mg SUBQ doses | 680mg | SUBQ | Q4W |

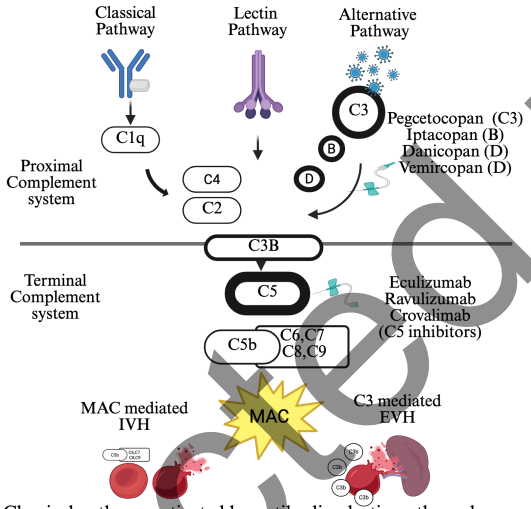
FDA: U.S. Food and Drug Administration; PNH: Paroxysmal nocturnal hemoglobinuria; IV: intravenous; SUBQ: subcutaneous; Q2W: once every 2 weeks; Q8W: once every 8 weeks; BIW: twice every week; BID: twice every day; TID: three times every day; Q4W: once every 4 weeks

**Table 2: Summary of clinical trials in PNH treatment**

| Drug | Trial Name | Cohort | Therapy Approach | BTH Rate | Thrombotic Events | FACIT-Fatigue Improvement | Hgb increase (g/dL) |
|---|---|---|---|---|---|---|---|
| **Eculizumab** | TRIUMPH | PNH w/ transfusion dependent | Monotherapy | 10.8 % | 0 | 6.4 | 1.4 |
| **Ravulizumab** | CHAMPION-301 | Treatment naïve | Monotherapy | 4.0% | 2/125* | 7.07 | Not reported § |
| | CHAMPION-302 | Eculizumab w/ persistent anemia | Monotherapy | 0.0% | 0 | 2.1 | Not reported § |
| **Pegcetacoplan** | PEGASUS | C5 inhibitor w/ persistent anemia | Monotherapy | 10.0 % | 0 | 9.2 | 2.37 |
| | PRINCE | Treatment naïve | Monotherapy | 0.0% | 0 | 7.8 | 2.9 |
| **Iptacopan** | APPLY | C5 inhibitor w/ persistent anemia | Monotherapy | 3.2% | 1/62† | 8.0 | 3.59 |
| | APPOINT | Treatment naïve | Monotherapy | 0.0% | 0 | Not reported | 3.87 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Danicopan** | ALPHA | C5 inhibitor w/ persistent anemia | Add-on | 8.3% | 0 | 7.9 | 2.94 |
| **Crovalimab** | COMMODOR E 2 | Treatment naïve | Monotherap y | 10.4 % | 0 | 7.8 | 2.2 |
| *One patient who was taking oral contraceptive developed deep vein thrombosis, and one patient discontinued anticoagulation at the initiation of the trial.<br>†Transient ischemic attack considered unrelated to iptacopan; iptacopan treatment is ongoing<br>§The ravulizumab trials report a hemoglobin stabilization rate (avoidance of a ≥2g/dL decrease in hemoglobin from baseline), the ravulizumab rate was noninferior to eculizumab in both trials | | | | | | | |

**Complement pathway and targets of therapies in PNH**




Classical pathway activated by antibodies, lectin pathway by ficolins or lectins and alternative by viral or bacterial surfaces. MAC: Membrane attack complex, IVH: Intravascular hemolysis,EVH: Extravascular hemolysis.