Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria

Final Evidence Report

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ICER Staff and Consultants	The University of Washington and University of Pittsburgh Modeling Group
Anil N. Makam, MD, MAS Associate Professor of Medicine University of California, San Francisco **Shahariar Mohammed Fahim, PhD** Research Lead Institute for Clinical and Economic Review **Belén Herce-Hagiwara, BA** Senior Research Assistant Institute for Clinical and Economic Review **Marina Richardson, PhD, MSc** Senior Health Economist Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** Special Advisor Institute for Clinical and Economic Review **Foluso Agboola, MBBS, MPH** Vice President of Research Institute for Clinical and Economic Review	**Kangho Suh, PharmD, PhD** Assistant Professor University of Pittsburgh **Josh J. Carlson, PhD, MPH** Professor University of Washington **Ronald Dickerson, MPH, M.Econ.** Research Assistant University of Washington School of Pharmacy *The roles of the University of Washington and the University of Pittsburgh are limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the views of the University of Washington or the University of Pittsburgh.*

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Anil Makam served as the lead author for the report. Shahariar Mohammed Fahim and Belén Herce-Hagiwara led the systematic review and authorship of the comparative clinical effectiveness section of this report. Josh J. Carlson and Kangho Suh developed the cost-effectiveness model and authored the corresponding sections of the report. Marina Richardson conducted analyses for the budget impact model. Foluso Agboola and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Becca Piltch, Grace Ham, and Yasmine Kayali for their contributions to this report.

About ICER

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

Expert Reviewers

Robert Brodsky, MD
Professor of Medicine
Johns Hopkins University
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Leigh Clark, BCPA
Director, Patient Services
Aplastic Anemia and MDS International Foundation (AAMDSIF)
AAMSDSIF receives greater than 25% of its funding from health care companies.

Doug Coyle, PhD
Professor
School of Epidemiology and Public Health, University of Ottawa
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Ilene Weitz, MD
Professor of Medicine
University of Southern California School of Medicine
Dr. Weitz served as a Principle Investigator for Pegcetacoplan PEGASUS and PHAROAH trials as well as a Principal Investigator for Iptacopan for PNH and aHUS. Dr. Weitz has also received honoraria in excess of $5,000 from Alexion Pharmaceuticals.

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback. For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2023/08/PNH_Stakeholder-List_For-Publication_08222023.pdf

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
ARC	Absolute reticulocyte count
BTH	Breakthrough hemolysis
CFB	Change from baseline
C5i	C5 inhibitor
DL	Deciliter
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-3L	EuroQoL five dimensions three-level version
EVH	Extravascular hemolysis
evLY	Equal value life years
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
g	Gram
g/dL	Grams per deciliter
HBPB	Health benefit price benchmarks
Hgb	Hemoglobin
HSCT	Hematopoietic stem cell transplantation
IV	Intravenous
L	Liters
LDH	Lactate dehydrogenase
MAVE	Major adverse vascular event
MCID	Minimal clinically important difference
Mg	milligram
n	Number
N	Total number
NA	Not available
NR	Not reported
PNH	Paroxysmal nocturnal hemoglobinuria
QALY	Quality Adjusted Life Years
RBC	Red blood cell
RCT	Randomized controlled trial
SD	Standard deviation
TBD	To be determined
U/L	Units per liter

Executive Summary

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder characterized by chronic destruction of red blood cells (hemolytic anemia) and blood clots (thrombosis).[1] Hemolytic anemia primarily manifests in fatigue, and if severe, requires lifelong dependence on blood transfusions. Thrombosis is the most common cause of death.[2,3] The prevalence of PNH is 10 to 20 per million.[4,5] PNH is primarily a disease of adults, without an association by sex, race, ethnicity, or geography.[6]

PNH is caused by uncontrolled activation of the complement pathway of the immune system which causes hemolysis (**Figure 1**).[7] C5 inhibitor therapy has transformed the disease by greatly reducing intravascular hemolysis (occurring within blood vessels), thrombosis, and death, with life expectancies similar to age-matched controls.[8-10] An FDA-approved intravenous C5 inhibitor (eculizumab infusions every 2 weeks or ravulizumab infusions every 8 weeks) is recommended by clinical experts for the treatment of symptomatic PNH, which comprise up to two-thirds of PNH patients.[4,6,10-12] [13] Ravulizumab is preferred over eculizumab because of the fourfold longer half-life with less breakthrough hemolysis and lower costs.[14,15] However, even with therapy, about 20% are transfusion-dependent because extravascular hemolysis (EVH) is a mechanistic consequent of C5 inhibitor therapy.[16]

Pegcetacoplan, a proximal complement inhibitor administered subcutaneously twice weekly, is another FDA-approved treatment option for PNH. Unlike C5 inhibitors, pegcetacoplan prevents both intra and extravascular hemolysis.[17,18] However, clinical experts largely use pegcetacoplan only for patients on a stable C5 inhibitor regimen who have clinically significant EVH given their concern for its greater risk of breakthrough intravascular hemolysis and potentially thrombosis.[16,19]

There are two first-in-class proximal complement inhibitors, Iptacopan and Danicopan. Iptacopan, an oral Factor B inhibitor taken twice daily, was approved by the FDA on December 6, 2023, for the treatment of all PNH patients. Danicopan, an oral Factor D inhibitor taken thrice daily, is being considered by the FDA for add-on therapy to a C5 inhibitor for only treatment-experienced patients on a stable C5 inhibitor regimen with clinically significant EVH.

Iptacopan was evaluated in two small 24-week trials. APPOINT-PNH, a single-arm trial of 40 treatment-naïve patients, found that most achieved substantial hematologic response (improved hemoglobin, transfusion avoidance, and fatigue). APPLY-PNH, an open-label RCT of 97 treatment-experienced patients with clinically significant EVH, similarly found improved hematologic response versus continuing a C5 inhibitor. Iptacopan achieved both co-primary endpoints of increased hemoglobin ≥2 g/dL from baseline (75% vs 0%) and level ≥12 g/dL (85% vs 0%) without transfusions. Iptacopan had few serious harms; 3.2% had breakthrough hemolysis and 1.6% had a thrombosis (versus 0% with thrombosis in the C5 inhibitor arm).

The evidence base for the efficacy of add-on Danicopan was derived from the ALPHA trial, a 12-week placebo-controlled RCT of 86 treatment-experienced patients with clinically significant EVH. At the time of the publication of this report, we have data only on approximately the first 75% of the randomized population (n=63). Add-on danicopan substantially improved hematologic response versus add-on placebo, including the primary endpoint of change in hemoglobin from baseline between groups (+2.4 g/dL, p<0.001), and secondary outcomes of increased hemoglobin ≥2 g/dL from baseline without transfusions (60% versus 0%) and less fatigue. Danicopan had few serious harms.

Because of differences in treatment options and trial designs, we rated the clinical evidence separately for treatment-naive and treatment-experienced PNH populations.

For Iptacopan, the two small studies of short duration did not assuage experts' concerns about the risk of breakthrough intravascular hemolysis and thrombosis. For treatment-naive PNH patients, we rate the evidence for iptacopan as insufficient ("I") given the lack of comparative efficacy data versus a C5 inhibitor, the consensus standard of care.

For treatment-experienced PNH patients on a stable C5 inhibitor with clinically significant EVH, we rate the evidence for iptacopan versus continuing a C5 inhibitor as promising for moderate to substantial net benefit but inconclusive ("P/I") because of the uncertainty about the long-term benefit and safety, particularly related to breakthrough hemolysis and the more consequential but less common complication of thrombosis. Additionally, while recognizing it's a more convenient oral formulation, given the lack of comparative efficacy data to pegcetacoplan, we rate the evidence for iptacopan versus pegcetacoplan as insufficient ("I").

For add-on Danicopan to a C5 inhibitor, patients and clinicians welcomed the dual protection against both intra and extravascular hemolysis plus the greater certainty of protection against thrombosis, although were concerned about the costs. Although the trial was small and of short duration, because it was well tolerated and combined with C5 inhibition, we rate danicopan added on to a C5 inhibitor for treatment-experienced PNH patients with clinically significant EVH as comparable or better than continuing a C5 inhibitor (C++). However, given the lack of comparative efficacy data, we rate the evidence of add-on danicopan to a C5 inhibitor versus pegcetacoplan as insufficient ("I").

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Population: Treatment Naïve to Complement Inhibitors		
Iptacopan	C5 Inhibitor	"I"
Population: Treatment-Experienced on Stable C5 Inhibitor Regimen with Clinically Significant EVH		
Iptacopan	C5 Inhibitor	"P/I"
Iptacopan	Pegcetacoplan	"I"
Danicopan + C5 Inhibitors	C5 Inhibitor	"C++"
Danicopan + C5 Inhibitors	Pegcetacoplan	"I"

We developed a de novo decision analytic model to estimate the cost-effectiveness of iptacopan versus ravulizumab and add-on danicopan versus ravulizumab alone in treatment-experienced patients with PNH with clinically significant extravascular hemolysis from a health care perspective.

Compared with ravulizumab, treatment with iptacopan resulted in small gains in QALYs and evLYs and equivalent Lys. At the annual placeholder price of $550,377 treatment with iptacopan would cost more than ravulizumab, resulting in an estimated incremental cost-effectiveness ratio of $1,368,000 per QALY or evLY gained. As discussed in greater detail in Section 6, ICER has concluded that in a situation where a large percentage of the traditional Health Benefit Price Benchmark (HBPB) comes from cost offsets of therapies that, themselves, have prices that are not believed to be aligned with benefits to patients, ICER will present ranges from shared savings calculations as the most appropriated HBPBs. We calculate that approximately 97% of the traditional HBPB for iptacopan come from offsetting the cost of C5 inhibitor therapies that, themselves, have prices that are not believed to be aligned with benefits to patients. Under the shared saving scenario with a $150,000 annual cap on cost offsets, the HBPB for iptacopan is $178,000 to $180,000 annually.

In the comparison of add-on danicopan to ravulizumab alone, treatment with add-on danicopan resulted in small gains in QALYs and evLYs and the same number of Lys. Using the annual placeholder price of $150,000, treatment with add-on danicopan resulted in substantially more costs. At the assumed placeholder price, the incremental cost-effectiveness ratio for add-on danicopan is $9,457,000 per QALY or evLY gained. The HBPB for danicopan used as add-on therapy to a C5 inhibitor, is an annual price of $12,300 to $13,100.

The appraisal committee votes on questions of comparative effectiveness and value, along with policy recommendations regarding pricing, access, and future research are included in the Report. Three key policy recommendation themes are highlighted below:

- Out-of-pocket costs and access are a concern given the need for indefinite treatment and the high costs of PNH therapies. Payers should ensure equitable out-of-pocket cost burden under the pharmaceutical benefit for newer oral therapies compared to existing C5 inhibitor infusions covered under the medical benefit. Payers should also eliminate annual coverage

renewal requirements or implement this policy using a separate time-sensitive pathway to avoid missed doses.

- Given great uncertainty about the longer-term safety and efficacy of newer treatment options, payers should be aware that clinicians and patients place a high value on shared decision making to choose between a C5 inhibitor and non-intravenous proximal complement inhibitor treatment options. To help fill these knowledge gaps, clinical societies should issue a treatment guideline to offer pragmatic advice about how to select among different therapies, and all stakeholders should contribute to registries to establish long-term safety and durability of newer treatments, and to enable comparative effectiveness research of different treatment strategies.
- The value of novel PNH therapies should not be determined exclusively by estimates of long-term cost offsets used in traditional cost-effectiveness analyses alone since the existing standard of care, C5 inhibitors, are priced significantly higher than cost-effective levels.

1. Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired blood disorder characterized by hemolytic anemia (i.e., chronic destruction of red blood cells) and thrombosis.[1] Hemolytic anemia primarily manifests in fatigue, and if severe, requires lifelong dependence on blood transfusions. Thrombosis, which occurs in up to 30% of PNH patients, is the most common cause of death in patients with PNH.[2,3]

PNH affects one to two persons per million with a prevalence of ten to 20 per million.[4,5] Although PNH can occur in children, PNH is primarily a disease of adults, with a median age of onset in the 30s, without an association by sex, race, ethnicity, or geography.[6]

PNH is caused by the deficiency of two proteins, CD55 and CD59, on the surface of precursor red blood cells in the bone marrow, which prevent destruction by a part of the immune system known as the complement pathway (**Figure 1**).[7] CD59 deficiency causes intravascular hemolysis by uncontrolled C5 activation in the terminal complement pathway, and accounts for most PNH manifestations. CD55 deficiency leads to extravascular hemolysis in organs like the spleen by uncontrolled C3 activation in the proximal complement pathway.

The introduction of the C5 inhibitor eculizumab in 2008, followed by ravulizumab in 2018, has transformed the disease by greatly reducing intravascular hemolysis, thrombosis, and death, with life expectancies similar to age-matched controls.[8-10] Because PNH is a chronic disease and C5 inhibitors are costly (about $500,000/year),[20] the lifelong costs of treatment are over $9 million dollars.[15]

Even with C5 inhibitor therapy, about one-third of patients have symptomatic anemia; and up to 20% are transfusion-dependent.[16] One major reason for this is because of the mechanistic consequence of C5 inhibitors which increase extravascular hemolysis due to uncontrolled C3 activation. Another major reason for persistent anemia is bone marrow failure, which is unrelated to complement activation.[21]

PNH is a clinical diagnosis confirmed by a peripheral flow cytometry blood test which counts the clone size—the number of cells that are affected by PNH. Clone size is the main determinant of severity—the greater the size the greater the hemolysis.[11] Clone size tends to be either very low or very high, with clinically significant intravascular hemolysis typically beginning at sizes greater than 50%.[11,22] Patients with PNH should also undergo a bone marrow biopsy to exclude bone marrow failure, namely aplastic anemia, which is the only known risk factor for PNH.

PNH is classified into three categories: subclinical, with bone marrow failure, and classic. The former two categories tend to have small clone sizes, and as such are asymptomatic or have modest symptoms. Classic PNH has large clone sizes with considerable hemolysis and thrombosis risk.

There are currently no clinical guidelines for PNH. Consensus statements and expert opinion recommend an intravenous anti-C5 monoclonal antibody approved by the FDA for the treatment of symptomatic PNH, which comprise up to two-thirds of PNH patients.[4,6,10-13] Ravulizumab is preferred over eculizumab because of the fourfold longer half-life (dosed every eight vs. two weeks) with less breakthrough hemolysis and lower costs.[14,15] Pegcetacoplan, a peptide administered subcutaneously twice weekly that inhibits C3, is another FDA-approved treatment option for PNH. Unlike C5 inhibitors, pegcetacoplan prevents both intra and extravascular hemolysis. [17,18] However, clinical experts largely use pegcetacoplan only for patients on a stable C5 inhibitor regimen who have clinically significant EVH given their concern for its greater risk of breakthrough intravascular hemolysis and potentially thrombosis due to its shorter half-life and its mechanism of action with the potential amplification effect of C3b on C5 activation (**Figure 1**).[16,19]

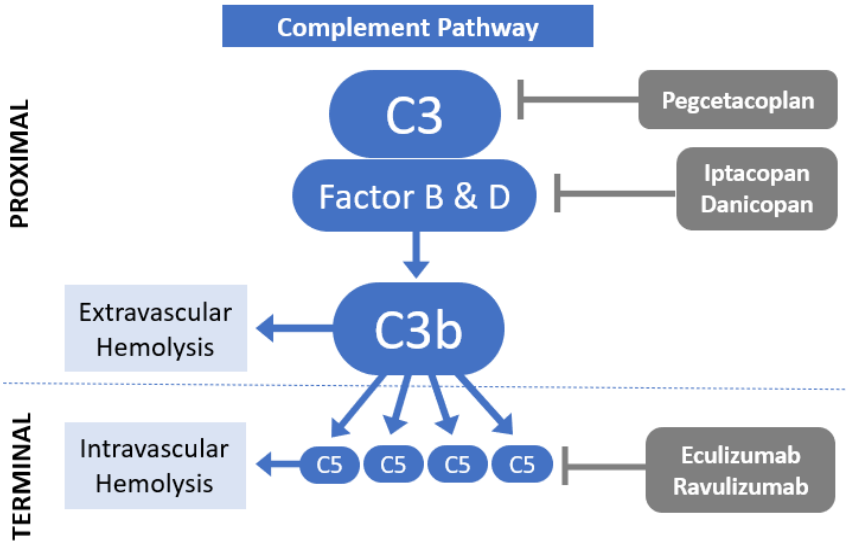
In addition to complement inhibition, patients should also receive supportive care, including blood transfusions for symptomatic anemia, blood thinners for thrombosis, and possibly short-courses of corticosteroids for hemolytic episodes.[4,10,12] Bone marrow transplant is the only cure for PNH, but because of its considerable morbidity and mortality, it is largely only recommended for patients with severe bone marrow failure.

In addition to the complement inhibitors already FDA-approved, there are additional agents in development, including two first-in-class proximal complement inhibitors, Iptacopan and Danicopan (**Table 1.1**). Iptacopan, an oral Factor B inhibitor taken twice daily for the treatment of all PNH patients, was approved by the FDA on December 6, 2023. Danicopan, an oral Factor D inhibitor taken thrice daily, is being considered by the FDA for add-on therapy to a C5 inhibitor for only treatment-experienced patients with clinically significant extravascular hemolysis. Given these potential different options, there is a need to understand the comparative benefits and costs of the treatments for PNH.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Iptacopan	Factor B Inhibitor	Oral capsule	200 mg twice daily
Danicopan	Factor D Inhibitor	Oral tablet	150-200 mg three times daily

Figure 1. Drugs Targeting The Complement Pathway



2. Patient and Caregiver Perspectives

ICER engaged with patients, representatives from the Aplastic Anemia and MDS International Foundation, and clinical experts to understand the perspectives from those living with the disease, their specific challenges and unmet needs, contextual considerations, and outcomes most relevant to patients and the PNH community (See Supplement Section B).

Patients, patient advocates, and clinical experts emphasized the diverse range of disease experiences, the careful consideration of the tradeoffs of improved convenience and quality of life from new therapies versus uncertain protection against life threatening complications, and concerns about the affordability and access to PNH drugs.

PNH is a highly heterogenous and unpredictable disease, ranging from no symptoms to severe hemolytic anemia with fatigue, and for some, life-threatening blood clots. While clone size is the greatest determinant of disease activity, patients with seemingly similar PNH burden can have different manifestations.[6,11] Even if severely symptomatic, patients and patient advocates described PNH as an "invisible" illness since they do not outwardly appear ill or require caregiver support. However, debilitating fatigue and worry about unpredictable thromboses can strain relationships and cause anxiety among loved ones.

Deciding between treatment options is highly individualized depending on a patient's disease activity and their preferences about treatment efficacy, safety, convenience, and cost.[23] Clinical experts uniformly recommend a C5 inhibitor for all patients with symptomatic disease or who are pregnant. Patients and patient advocates we spoke to were satisfied with current C5 inhibitor therapy for disease control, protection against thrombosis, and peace of mind of not worrying about missing doses; and described acceptable lifestyle adaptations, such as rearranging travel plans to accommodate scheduled infusions every two or eight weeks depending on the type of C5 inhibitor. Infusions are typically done through a peripheral vein without the need for invasive vascular ports or a central venous catheter.

While C5 inhibitor therapy has transformed the experience of living with PNH,[8] patients may prioritize the convenience of non-intravenous therapies that can also improve quality of life via less hemolysis, transfusion dependence, and fatigue. Although approved by the FDA in 2021, few patients take the proximal complement inhibitor, pegcetacoplan, in part because of the difficulty and discomfort of the twice weekly on-body subcutaneous administration, the risk of breakthrough intravascular hemolysis due to nonadherence or a major stressor (infection or surgery), and the uncertain protection against thromboses as compared with the decade-plus real-world experience of C5 inhibitors. However, if patients on a stable C5 inhibitor regimen were experiencing clinically significant EVH, clinical experts and patients we spoke to would consider switching to pegcetacoplan, especially in the absence of a prior thrombosis. Stakeholders were enthusiastic for

alternate oral proximal complement inhibitors, however, were concerned about their very short half-life with risk for breakthrough hemolysis due to missing even a few doses.

Patients, patient advocates, and clinical experts uniformly expressed concern about the access and affordability of PNH treatments since patients require lifelong therapy. While the initial diagnosis of PNH can be considerably delayed since it is a rare disease, once diagnosed patients and patient advocates, we spoke with expressed little trouble seeing a hematologist with expertise in PNH and accessing a specialty pharmacy and infusion center for C5 inhibitor therapy. However, accessibility may be a larger issue for patients living in more remote rural areas which require greater travel. Thus, oral therapies may provide another option to overcome these barriers. Another concern that was raised was the burdensome annual reauthorization process for complement inhibitor therapy with insurers, which has led to missed doses. Finally, patients expressed concern for greater out-of-pocket costs for proximal complement inhibitor medications which would be covered by their insurers' pharmaceutical benefit, versus C5 inhibitor infusions, which are covered by the medical benefit.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Detailed methods for the systematic literature review assessing the evidence on iptacopan and danicopan for the treatment of PNH are available in Supplement Section D1.

Scope of Review

We reviewed the clinical effectiveness of iptacopan monotherapy and danicopan add-on to a C5 inhibitor for the treatment of PNH. C5 inhibitor therapy (i.e., eculizumab and ravulizumab) and pegcetacoplan were considered as the comparators. We sought evidence for iptacopan and danicopan versus comparators of interest in January 2024 on patient important outcomes including fatigue, anemia (as measured by hemoglobin level), red blood cell transfusions, thrombosis, and other biomarkers of blood cell destruction (hemolysis) such as lactate dehydrogenase (LDH) levels and absolute reticulocyte count. The full scope of the review is available in Supplement Section D1.

Evidence Base

Evidence informing our review of iptacopan for PNH was derived from two Phase 3 trials, one conducted in the treatment-naive (APPOINT-PNH) and one in the treatment-experienced population (APPLY PNH).[24-31] One additional reference of a Phase 2 trial was included to contribute to the safety profile of iptacopan.[32] The FDA integrated review document on iptacopan was also incorporated (available from the FDA website as of its approval on December 6, 2023).[33]

Evidence informing our review of danicopan added on to a C5 inhibitor was primarily derived from one peer-reviewed publication, three abstracts, and data posted on clinicaltrials.gov from the Phase 3 ALPHA trial conducted in the treatment-experienced population.[34-38] One additional reference of a Phase 2 trial was included to inform the safety profile of danicopan.[39]

None of the identified studies compared either iptacopan or danicopan added on to a C5 inhibitor to pegcetacoplan monotherapy. As such, we searched for trials of pegcetacoplan separately. We included the Phase 3 PEGASUS trial of pegcetacoplan conducted in the treatment-experienced PNH population as part of our evidence base. Details of the PEGASUS trial are described in Supplement Tables D3.1.-D.3.6.[2]

Given differences in treatment options and trial designs, we present comparative clinical effectiveness data separately for two related but distinct populations of PNH: patients who are treatment-naive to complement inhibitors (applicable to iptacopan only) and patients who are

treatment-experienced on a stable regimen of a C5 inhibitor but have clinically significant extravascular hemolysis (EVH).

Treatment-Naive to Complement Inhibitors

Iptacopan

One trial provided evidence for iptacopan in patients with PNH treatment-naive to a complement inhibitor: APPOINT-PNH, a Phase 3, multinational, open-label, single-arm trial. The trial enrolled adults who had a confirmed diagnosis of PNH with hemolysis, as defined by a clone size ≥ 10%, mean hemoglobin level <10 g/dL, LDH >1.5 times the upper limit of normal, and no prior treatment with a complement inhibitor. Participants with a history of bone marrow failure, hematopoietic stem cell transplantation (HSCT), or those with known or suspected hereditary complement deficiency were excluded. The primary endpoint was hematological response, defined as an increase in hemoglobin of ≥2 g/dL from baseline in the absence of RBC transfusions.[40] See Table 3.1.

Investigators enrolled 40 participants after a screening period of 8 weeks to receive a dose of 200 mg iptacopan taken orally twice daily for 24 weeks. Participants had a mean age of 42 years, an average of five years diagnosis duration, and a mean hemoglobin of 8.2 g/dL at baseline. A majority of participants (70%) received RBC transfusion in the prior six months.[26] Additional baseline characteristics can be found in Table 3.2. and Supplement Table D3.2.

Treatment-Experienced with Clinically Significant EVH

Iptacopan

The key trial providing evidence for iptacopan in treatment experienced PNH patients with clinically significant EVH is the Phase 3 APPLY-PNH trial. APPLY-PNH was a multinational, open-label, randomized controlled trial comparing the effectiveness of iptacopan versus continuing C5 inhibitor monotherapy in PNH patients treated with C5 inhibitors who had clinically significant EVH. Patients were included if they had clone size ≥10%, mean hemoglobin <10 g/dL, a reticulocyte count ≥ 100 × 10^9 cells/L, and were on a stable regimen of eculizumab or ravulizumab for ≥ 6 months prior to randomization. Participants on a stable eculizumab dose but with a dosing interval of 11 days or less, a history of bone marrow failure, HSCT, or known or suspected hereditary complement deficiency were excluded. The co-primary endpoints were hematological responses defined using two different cut-points for hemoglobin level: an increase of ≥2 g/dL from baseline or maintenance of ≥12 g/dL in the absence of RBC transfusions at the end of the 24 week treatment period.[41] See Table 3.1.

Of 97 enrolled participants, 62 were randomized to 200 mg of iptacopan taken orally twice daily, and 35 continued treatment with a maintenance dose of eculizumab (n=23, 66%) administered

intravenously twice weekly or ravulizumab (n=12, 34%) administered every eight weeks. Baseline characteristics were similar between arms. APPLY-PNH trial participants had a mean age of 51 years, a mean duration of 13 years since diagnosis, and a mean hemoglobin level of 8.9 g/dL at baseline. Over half of the enrolled participants received RBC transfusions in the six months prior to randomization. The baseline prevalence of thrombotic events was not reported.[28] See Table 3.2. and Supplement Table D3.2.

Danicopan

The key trial providing evidence for danicopan in the treatment experienced PNH patients with clinically significant EVH was the Phase 3 ALPHA trial. ALPHA is a multinational, double-blind, placebo-controlled, randomized trial comparing the efficacy of danicopan add-on to a C5 inhibitor versus placebo add-on to a C5 inhibitor in PNH patients with clinically significant EVH. Participants were enrolled in the trial if they had a hemoglobin level ≤9.5 g/dL, absolute reticulocyte count ≥120 × 10^9/L, and were receiving an approved C5 inhibitor for at least the prior six months. Patients with a history of bone marrow failure, HSCT, and hereditary complement deficiency were excluded. Randomization was stratified by transfusion history (>2 vs. ≤ 2 transfusions), hemoglobin (<8.5 g/dL vs. ≥8.5 g/dL), and enrollment from Japan. The primary endpoint was least squares mean change from baseline in hemoglobin level at week 12.[35,36] See Table 3.1.

A total of 86 patients were randomized 2:1 to add-on danicopan (N=57) versus add-on placebo (N=29) for 12 weeks.[35] The available pre-specified interim efficacy analysis included in this report only included approximately the first 75% of randomized patients (N=63). Additional patients were included in the safety analysis. Baseline characteristics were available for all randomized participants and were comparable between arms. The mean age was over 50 years for both arms and mean hemoglobin at baseline was 7.7 g/dL and 7.9 g/dL for the danicopan and placebo arms, respectively. All participants received ≥1 RBC transfusion in the 6 months prior to randomization. The danicopan arm included more ravulizumab users versus the placebo arm. Baseline prevalence of thrombotic events was not reported.[34,36] See Table 3.2.

Additional details on all these trials (APPOINT-PNH, APPLY-PNH, and ALPHA) and their baseline characteristics can be found in Supplement Tables D3.1. and D3.2.

Table. 3.1. Overview of Key Phase 3 Trials of Iptacopan and Danicopan

Trial	Treatment & Design	N	Included Population	Primary Outcome
Population: Treatment-Naïve to Complement Inhibitors				
APPOINT-PNH[40]	**Iptacopan** *single arm*	40	• Adults with PNH with clone size ≥10% • Hemoglobin (Hb) <10 g/dL • LDH >1.5 × upper limit of normal • No prior treatment with a C5i	• Hb ≥2 from baseline without transfusion at 24 weeks
Population: Treatment-Experienced with Clinically Significant EVH				
APPLY-PNH[41]	**Iptacopan** vs. C5i *8:5, open-label*	97	• Adults with PNH and clone size ≥10% • Clinically significant EVH: - Hemoglobin (Hb) <10 g/dL - Reticulocyte count ≥100 × 10^9 cells/L • Treatment with a C5i for ≥6 months	• Increase from baseline in Hb of ≥2 g/dL or sustained ≥12 g/dL, without RBC transfusions at 24 weeks
ALPHA[35]	**Danicopan + C5i** vs. Placebo + C5i *2:1, double-blind*	86	• Adults with PNH • Clinically significant EVH: - Hemoglobin (Hb) ≤9.5 g/dL - Reticulocyte count ≥120 × 10^9 cells/L • Treatment with a C5i for ≥6 months	• Change from baseline in Hb at 12 weeks

C5i: C5 inhibitors, EVH: extravascular hemolysis, Hb: hemoglobin, g/dL: grams per deciliter, L: liter, LDH: lactate dehydrogenase, N: number, PNH: paroxysmal nocturnal hemoglobinuria, RBC: red blood cell

Table. 3.2. Key Baseline Characteristics of Iptacopan and Danicopan Phase 3 Trials

C5 Inhibitor Experience		Naïve	Experienced			
Trial		APPOINT-PNH	APPLY-PNH		ALPHA	
Treatment Arm		Iptacopan	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i
N		40	62	35	57	29
Age, years	Mean (SD)	42.1 (15.9)	51.7 (16.9)	49.8 (16.7)	52.8 (NR)	52.9 (NR)
Sex, n (%)	Female	17 (42.5)	43 (69.4)	24 (68.6)	34 (59.6)	20 (69)
Race, n (%)	Asian	27 (67.5)	NR	NR	22 (38.6)	10 (34.5)
	White	12 (30)			28 (49.1)	14 (48.3)
	Others/NR	1 (2.5)			7 (12.3)	5 (17.2)
C5 Inhibitors, n (%)	Eculizumab	N/A	40 (64.5)	23 (65.7)	21 (36.8)	14 (48.3)
	Ravulizumab	N/A	22 (35.5)	12 (34.3)	36 (63.2)	15 (51.7)
Time since Diagnosis, Years (SD)		4.7 (5.5)	11.9 (9.8)	13.6 (10.9)	NR	NR
Mean Hemoglobin (SD), g/dL		8.2 (1.1)	8.9 (0.7)	8.9 (0.9)	7.7 (0.95)	7.9 (1.0)
Mean LDH† (SD), IU/L		1,582 (NR)	269 (70)	273 (85)	304 (124)	286 (93)
Mean ARC‡ (SD), 10^9 cells/L		154 (64)	193 (84)	191 (81)	248 (97)	223 (115)
Mean FACIT-Fatigue Score (SD)		*32.8*	*34.7*	*30.8*	34.2 (11)*	33.6 (10.7)*
RBC Transfusion, N (%)		28 (70)	35 (56.5)	21 (60.0)	49/49 (100)*	24/24 (100)*

Italicized data have been digitized from figures; interpret with caution.

ARC: absolute reticulocyte count, g/dL: grams per deciliter, N/A: not applicable, NR: not reported, PNH: paroxysmal nocturnal hemoglobinuria, RBC: red blood cell, SD: standard deviation

* Data only provided for 49 danicopan treated patients and 24 placebo arm patients.

† Normal range for LDH is around 140 to 280 U/L.[42]

‡ Normal range for ARC is around 25×10^9/L and 150×10^9/L.[43]

3.2. Results

Clinical Benefits

Here we describe the results from trials of iptacopan (APPOINT-PNH and APPLY-PNH) and danicopan (ALPHA) in achieving their primary and secondary endpoints which focus on hematologic response (hemoglobin level, transfusions, biomarkers of hemolysis) and the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue). All three trials assessed other measures of health-related quality of life as exploratory endpoints. Thrombotic events and breakthrough hemolysis were considered adverse events in the clinical trials, and as such, are described in the Harms section.

Treatment-naïve to Complement Inhibitors

Evidence on iptacopan's efficacy in patients with PNH who were treatment-naïve to complement inhibitors was derived from the single-arm APPOINT-PNH trial. Of 40 participants, 7 (18%) missed follow-up visits between week 18 and 24 primarily due to COVID infection or pandemic-related policies. As such, not every patient contributed to every outcome evaluated.

Hemoglobin Outcomes and Transfusion Avoidance

In the APPOINT-PNH trial, the primary endpoint was hematological response, defined as an increase in hemoglobin of ≥2 g/dL from baseline in the absence of RBC transfusions.[40] Among the 33 participants with available data, 31 (94%) achieved the primary endpoint of a sustained hemoglobin ≥2 g/dL in the absence of RBC transfusions. Over half of these 33 participants (58%) also sustained levels of hemoglobin ≥12 g/dL without transfusions. An improvement in hemoglobin was observed as early as the first week of treatment, with a mean hemoglobin of 12.6 g/dL at week 24. All 40 participants achieved transfusion-avoidance assessed between week 2 and 24.[26]

Lactate Dehydrogenase (LDH) Level

In the APPOINT-PNH trial, the percent change from baseline in LDH was measured as a secondary endpoint as increased concentrations of LDH are a biomarker of intravascular hemolysis.[40,9] On average, LDH levels decreased within the first week of treatment to a mean level of 261 U/L at 24 weeks, with around 95% of participants achieved LDH levels ≤1.5 times the upper limit of normal.[24,26]

Patient-Reported Outcome: Fatigue and Quality of Life

Self-reported fatigue, as measured by the FACIT-Fatigue score, improved from baseline by a mean of 10.8 points (95% CI 8.67, 12.8) at 24 weeks;[26] greater than the suggested minimal clinically important difference (MCID) of five points in patients with PNH.[44] In an exploratory analysis, an

estimated 41% to 55% of the trial participants surpassed the predetermined subscale-specific thresholds of meaningful response in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scale.[31]

See Table 3.3. and Supplement Tables D3.3.–D3.5. for more details.

Table 3.3. Key Trial Results for Treatment-Naïve to Complement Inhibitor Population

Key Endpoints at 24 weeks	APPOINT-PNH N=40
Increase in hemoglobin ≥ 2g/dL without transfusions – n/N (%)	31/33* (94)
Sustained hemoglobin ≥ 12g/dL without transfusions – n/N (%)	19/33* (58)
Hemoglobin level, g/dL – mean change from baseline (95% CI)	4.3 (3.9, 4.7)
Achievement of RBC transfusion avoidance – n/N (%)	40/40 (100)
Lactate dehydrogenase level, U/L – mean (SD)	261 (89)
FACIT-Fatigue score – mean change from baseline (95% CI)	10.8 (8.7, 12.8)

95% CI: 95 percent confidence interval, FACIT: Functional Assessment of Chronic Illness Therapy, g/dL: grams per deciliter, n: number, N: total number, RBC: red blood cell, SD: standard deviation, U/L: units per liter
* 7 participants with missing data between weeks 18 to 24 were not evaluable.

Treatment-Experienced with Clinically Significant EVH

Iptacopan

Evidence for iptacopan's efficacy in patients with PNH who are treatment-experienced on a stable regimen of a C5 inhibitor but still experience clinically significant EVH came from APPLY-PNH: a Phase 3, open-label, randomized trial. See Table 3.4. and Supplement Tables D3.3.–D3.5, D3.7. for more details.

Hemoglobin Outcomes and Transfusion Avoidance

In APPLY-PNH, the co-primary endpoints were hematological responses defined using two different cut-points for hemoglobin level: an increase of at least 2 g/dL from baseline or levels sustained at or above 12 g/dL in the absence of RBC transfusions at the end of 24 weeks of treatment.[41] Approximately 85% of patients in the iptacopan arm achieved an increase in hemoglobin from baseline of ≥2g/dL and 70% of iptacopan-treated patients sustained hemoglobin levels ≥12 g/dL without RBC transfusions. In contrast, none of the participants assigned to a C5 inhibitor achieved these endpoints. From baseline, iptacopan increased mean hemoglobin levels by 3.7 g/dL (95% CI 3.2, 4.1; p<0.0001) more compared to the C5 inhibitor arm. Iptacopan also achieved greater transfusion avoidance during weeks 2 and 24 or treatment compared to the C5 inhibitor arm (95% vs. 40%).[28,33]

Lactate Dehydrogenase (LDH) Level

LDH levels were measured as a secondary endpoint in the APPLY-PNH trial.[41] Although the iptacopan arm had a lower mean LDH level within the first few weeks of treatment, it was not statistically significantly lower than the C5 inhibitor arm in the later phase of the 24-week treatment period.[28]

Patient-Reported Outcome: Fatigue and Quality of Life

Iptacopan improved fatigue at week 24 above the suggested MCID value of five for the FACIT-Fatigue measure: an 8.6-point improvement from baseline versus a <1-point improvement in the C5 inhibitor arm (95% CI 5.3, 11.3, p<0.001).[28] An exploratory responder analyses suggested that iptacopan led to meaningful improvements in EORTC QLQ C30 subscales (39% to 49% responders in the iptacopan arm vs. 9% to 20% responders in the C5 inhibitor arm; p<0.01).[31]

Extension Phase Durability

During a 24-week uncontrolled extension period with 97% participant retention, the above findings were sustained for the iptacopan arm, with comparable beneficial trends observed for the C5 inhibitor arm who were switched to iptacopan. See Supplement Table D3.7.

Danicopan

Efficacy of danicopan in patients with PNH who are treatment-experienced on a stable regimen of a C5 inhibitor but still experience clinically significant EVH came from ALPHA: a Phase 3, double-blind, placebo-controlled, randomized trial.

Hemoglobin Outcomes and Transfusion Avoidance

The primary endpoint of the ALPHA trial was the least squares mean change from baseline in hemoglobin levels at week 12 of treatment.[35] At the time of the report, data were available for 63 of 86 total randomized participants (approximately 75% of the overall enrollment target in a protocol prespecified interim efficacy analysis set). Treatment with danicopan added on to a C5 inhibitor resulted in a statistically significant and clinically meaningful improvement in hemoglobin levels from baseline compared to placebo-add on group (between-group difference: +2.4 g/dL, 95% CI 1.7, 3.2, p<0.001). Danicopan-add on treatment also significantly improved hematologic response: more participants achieved an increase of at least 2 g/dL in hemoglobin from baseline without requiring RBC transfusions (60% vs. 0% in the placebo-add on group). More participants treated with danicopan add-on treatment achieved transfusion avoidance during the 12-week trial period than in the placebo add-on group (83% vs. 38%).[34,36] See Table 3.4. and Supplement Tables D3.3. for more details.

Lactate Dehydrogenase (LDH) Level

Mean LDH levels were measured as a secondary endpoint in the ALPHA trial. [35] At the end of 12-weeks, participants treated with danicopan add-on achieved greater least squares mean change in LDH from baseline than those in the placebo add-on arm (-23.5 U/L vs. -2.9 U/L). Although the treatment difference was not statistically significant, both arms maintained near-normal LDH levels.[35,36,37]

Patient-Reported Outcomes: Fatigue & Quality of Life

Fatigue, as measured by the FACIT-Fatigue score, significantly improved in the danicopan add-on group above the MCID value of five points but did not meaningfully improve in the placebo add-on arm (+8.0 points vs. +1.9 points; p=0.002).[34,36] The changes from baseline in the exploratory measure of EuroQoL five dimensions three-level version (EQ-5D-3L) scores were similar in both arms at week 12. In an exploratory analysis conducted at week 12, the danicopan add-on arm demonstrated statistically significant improvements over the placebo add-on arm in physical functioning, social functioning, and fatigue subscales of the EORTC QLQ-C30 scale.[36] Results for additional patient-centered exploratory endpoints of work productivity and health care resource utilization are shown in the Supplement. See Table 3.4. and Supplement Tables D3.5 for more details.

Extension Phase Durability

During a 12-week uncontrolled extension period that included 93% of the ALPHA trial participants, the findings described above were sustained in the danicopan add-on group, with comparable beneficial trends observed for patients in the placebo add-on group who switched to danicopan add-on. See Supplement Table D3.7.

Table 3.4. Key Trial Results: Treatment-Experienced with Clinically Significant EVH Population

Trial	APPLY-PNH		ALPHA	
Arms	**Iptacopan (N=62)**	**C5i (N=35)**	**Danicopan + C5i (N=42)**	**Placebo + C5i (N=21)**
Increase in Hb ≥2g/dL – n/N (%)	51/60† (85)	0/35 (0)	25/42 (60)	0/21 (0)
Hb level ≥12g/dL – n/N (%)	42/60† (70)	0/35 (0)	NR	NR
Hb level – mean CFB (95% CI)	3.6 (3.3, 3.9)	-0.1 (-0.4, 0.4)	2.9 (0.2)*	0.5 (0.3)*
Treatment difference (95% CI); *P* value	3.7 (3.2, 4.1); *P* < 0.0001		2.4 (1.7, 3.2); *P* < 0.0001	
Achieved transfusion avoidance – n/N (%)	59/62 (95.2)	14/35 (40)	35/42 (83.3)	8/21 (38.1)
LDH level, U/L – mean (SD)	277 (117)*	283 (127)*	268 (61)	328 (224)
FACIT-Fatigue – mean CFB (95% CI)	8.6 (6.7, 10.5)	0.3 (-2.2, 2.8)	8.0 (1.1)*	1.9 (1.6)*
Treatment difference (95% CI); *P* value	8.3 (5.3, 11.3); *P* < 0.0001		6.1 (2.3, 9.9); *P* = 0.0021	

C5i**:** C5 inhibitor, CFB: change from baseline, CI: confidence interval, EVH: extravascular hemolysis, FACIT: Functional Assessment of Chronic Illness Therapy, g/dL: grams per deciliter, Hb: hemoglobin, LDH: Lactate dehydrogenase, n: number, N: total number, NR: not reported, SD: standard deviation, U/L: units per liter
* Digitized, interpret with caution
† 2 participants had missing data from week 18 to 24 and were not evaluable

Indirect Evidence: Iptacopan versus Danicopan versus Pegcetacoplan

In the absence of head-to-head trials comparing the proximal complement inhibitors (iptacopan, danicopan, and pegcetacoplan) to each other, we explored conducting a network meta-analysis to indirectly compare these therapies using the C5 inhibitor monotherapy arm in the respective trials as the anchor. However, the limited number of studies, as well as notable differences in the baseline characteristics of trial participants (hemoglobin level, LDH, transfusion dependence, type of C5 inhibitor), trial duration, and outcome definitions (hematologic response and transfusion avoidance) precluded this comparison. See Supplement Tables D3.1-D3.2 for more detail.

Harms

The safety profiles of iptacopan and danicopan were combined for all PNH patients where applicable since there was no rationale suggesting variability in harms across the two different PNH populations. We also included safety data from Phase 2 trials of iptacopan and danicopan described in Supplement Section D2.

Iptacopan

Safety of iptacopan was evaluated in APPOINT-PNH and APPLY-PNH over 24 weeks. Approximately 10% of participants receiving iptacopan in both trials experienced a serious adverse event, compared to 14% in the C5 inhibitor group of the APPLY-PNH trial. COVID-19 was the most frequent among these events. No participants in either trial had meningococcal infection, died, or discontinued therapy. The most frequent adverse events for iptacopan were headaches and diarrhea. More participants in the iptacopan arm experienced abdominal pain, arthralgia, dizziness, nasopharyngitis, nausea, and urinary tract infection compared to the C5 inhibitor arm. Fewer

iptacopan participants had COVID-19. [26,28] There was one death in the iptacopan arm due to an encapsulated bacterial infection during the APPLY rollover extension period.[33]

Breakthrough Hemolysis

The FDA review pooled 170 participants treated with at least one dose of iptacopan from APPLY-PNH, APPOINT-PNH, three other Phase 2 studies, and their corresponding rollover extension phase. Overall, the occurrence of BTH was lower in the pooled iptacopan arm (n=9, 5%) compared to the C5 inhibitor arm (n=8, 23%). However, data on breakthrough hemolysis rates were not available by the type of C5 inhibitor therapy, which is important as ravulizumab is known to have lower rates than eculizumab but only comprised about one-third of the C5 inhibitor arm. There was no discontinuation due to clinical BTH in the iptacopan arm.[33] Additional details regarding BTH can be found in Supplement Section D2.

Major Adverse Vascular Events (MAVE)

In the APPLY-PNH trial, one participant (1.6%) receiving iptacopan experienced a MAVE during treatment period.[41] No occurrences of MAVEs were reported in the C5 inhibitor arm of the APPLY-PNH trial or in the iptacopan arm of the APPOINT-PNH trial at the end of treatment period.[40,41] See Supplement Table D3.6. for additional harms.

Danicopan

Safety data for danicopan was sourced from clinicaltrial.gov for the Phase 3 ALPHA study of 86 treatment-experienced patients with PNH, which included the most comprehensive data on harms and tolerability.[35] Data was also sourced from a conference abstract which included all 80 participants exposed to danicopan during the trial.[37]

In the randomized treatment period, four participants discontinued the trial, three of whom were due to adverse events, two (3.5%) in the danicopan arm versus one (3.4%) in the placebo arm. Additionally, there was one discontinuation in the extension phase.[37] Serious adverse events occurred in five trial participants (three in danicopan arm and two in placebo arm), all deemed unrelated to the study drug. There was no meningococcal infection, death, or hemolysis-related discontinuation. Compared to the danicopan add-on arm, a higher proportion of the placebo-add on arm experienced nausea, diarrhea, contusions, and increased aspartate aminotransferase concentrations.[35] See Supplement Table D3.6. for additional harms.

Breakthrough Hemolysis (BTH)

Two (4.1%) participants in the danicopan add-on arm experienced non-serious hemolysis compared to none in the placebo group. In the additional safety assessment with all 80 danicopan exposed participants, four BTH events were reported in total, with only one potentially meeting the clinical definition of BTH without treatment discontinuation.[37]

Major Adverse Vascular Events (MAVE)

Data on the occurrence of MAVEs were not reported in the ALPHA trial.

Subgroup Analyses and Heterogeneity

For iptacopan, subgroup analyses for key prognostic factors (i.e., transfusion dependence, type of C5 inhibitor, and history of MAVE) from FDA review documents of the APPLY-PNH and APPOINT-PNH trials suggested similar efficacy as the overall results. However, findings should be interpreted cautiously given the small sample size and exploratory nature of analyses.[33]

There were no data provided for specific subgroups in the ALPHA trial.

Uncertainty and Controversies

There are a number of uncertainties for both iptacopan and danicopan given an emerging evidence base consisting of a handful of small-scale, short-term clinical trials conducted largely in countries outside of the US with potentially different standards of care.

Iptacopan: Treatment-Naïve and Treatment-Experienced PNH Populations

- The generalizability of iptacopan trials to the PNH populations in the US is uncertain, especially given the absence of an available consort diagram showing recruitment and screening, as well as a lack of details regarding the background standard of care for PNH in other countries.
- The evidence for iptacopan for treatment-naive PNH patients comes from a small single-arm trial of 24-week duration without a comparator group. Thus, we lack comparative efficacy of iptacopan versus a C5 inhibitor.
- For treatment-experienced PNH patients with clinically significant EVH, we lack quantitative comparisons of iptacopan versus pegcetacoplan. Qualitatively, although proximal complement inhibitors target different molecules and the severity of PNH among participants differed slightly across trials, they seem to share a common hematologic response in reducing hemolysis, blood transfusions, and fatigue, and improving hemoglobin. Further study is required to comparatively assess the efficacy of these strategies.
- There remains concern for more frequent and severe breakthrough intravascular hemolysis compared to C5 inhibitors due to the amplification effect of incomplete C3b inhibition (see

Figure 1) from medication nonadherence (given iptacopan's short half-life), complement-amplifying conditions (pregnancy, infections, major surgery), and potentially from the observed increased PNH clone size common to proximal complement inhibitor therapy. While the rates were low in the trials, they were of short duration (24 weeks) and may not be reflective of long-term use in real-world settings, particularly where adherence may be lower and complement-activating stressors may be more frequent (surgery, infections, pregnancy).

- Although the incidence of MAVEs was notably low for iptacopan in the trials, there is uncertainty regarding its durability for protecting against thrombosis. This concern is especially pertinent for treatment-naive patients since patients and clinical experts we spoke to highly valued the greater certainty of thrombosis protection from the 15 years of real-world experience and accrued effectiveness data of C5 inhibitor therapy.
- For the treatment-experienced population, the open-label trial design may have biased self-reported fatigue, decisions for blood transfusions, and clinically defined outcomes such as breakthrough hemolysis, MAVEs, or serious adverse effects. However, hematologic profiles are more bias-resistant to the open-label design.
- For the treatment-naive population, 18% of the 40 participants were missing a hemoglobin value at the end of the study period, so hematologic response could depend on whether there was informative censoring. However, all 40 participants avoided blood transfusions at some point during the study period, suggesting ample hematologic response.

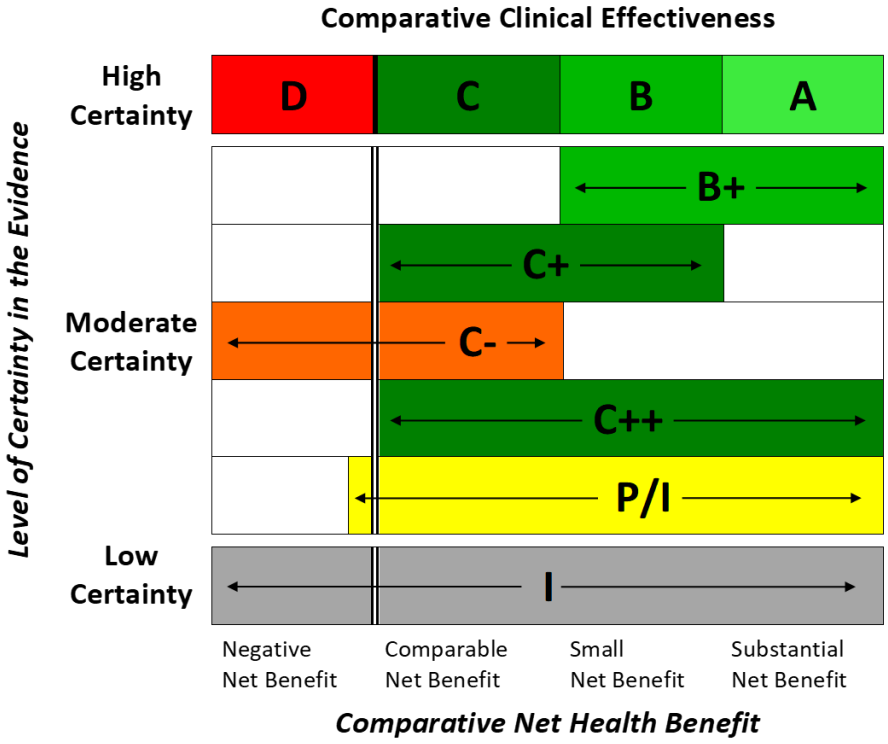
Danicopan Added-On to a C5 Inhibitor for the Treatment-Experienced PNH Population

- As described above, the generalizability of the ALPHA trial to the US population is uncertain. At the time of the publication of this report, we only had efficacy data for approximately the first 75% of the randomized population. Given the small sample size, it is possible the additional randomized data may skew results merely due to chance.
- We lack quantitative comparisons of danicopan added-on to a C5 inhibitor versus pegcetacoplan monotherapy. Qualitatively, although these proximal complement inhibitors target different molecules and the severity of PNH among participants differed slightly across trials (most severe for ALPHA trial), they seem to share a common hematologic response in reducing hemolysis, blood transfusions, and fatigue, and improving hemoglobin. Further study is required to comparatively assess the efficacy of these strategies.
- Of note, unlike for iptacopan or pegcetacoplan, breakthrough intravascular hemolysis and MAVEs are not a concern for danicopan since it is added to a C5 inhibitor, the latter of which will continue to provide protection against these complications that may arise with proximal complement inhibitors alone.
-

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D= "Negative" *- High certainty of an inferior net health benefit*
B+= "Incremental or Better" *– Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" *– Any situation in which the level of certainty in the evidence is low*

Treatment-Naïve PNH Patients

Iptacopan versus C5 Inhibitor

The APPOINT-PNH trial demonstrated substantial benefits for iptacopan in reducing blood transfusions and increasing hemoglobin levels and a clinically meaningful but more modest improvement in fatigue. However, our rating was tempered because the evidence is based on a single small study of short duration (24 weeks) without an active control arm which limited our ability to assess the comparative efficacy versus a C5 inhibitor, the consensus standard of care. Although well tolerated in the clinical trials, as for all proximal inhibitor therapies, there remain concerns for breakthrough intravascular hemolysis and inadequate protection against thrombosis, the major cause of morbidity and mortality in PNH. Coupled with uncertainty in generalizability and the lack of comparative efficacy data, we rate the evidence for iptacopan for the treatment of PNH patients naive compared to a complement inhibitor as insufficient (I).

Treatment-Experienced PNH Patients with Clinically Significant EVH

Iptacopan versus C5 Inhibitor

The open-label APPLY-PNH trial similarly demonstrated significant benefits for hemoglobin, blood transfusions, and fatigue for the narrower population of treatment-experienced PNH patients who had clinically significant EVH compared to continuing a stable regimen of a C5 inhibitor. However, given the uncertainty about the long-term benefit and safety, particularly related to breakthrough hemolysis and the more consequential but less common complication of thrombosis, we rate the net health benefit of switching to iptacopan versus continuing a C5 inhibitor as "Promising but Inconclusive" (P/I).

Danicopan plus C5 Inhibitor Versus C5 Inhibitor Only

The double-blind, placebo-controlled ALPHA trial demonstrated substantial benefits for danicopan added-on to a C5 inhibitor in reducing blood transfusions and increasing hemoglobin levels and a clinically meaningful but more modest improvement in fatigue. However, our rating was tempered because the evidence is based on a single small study of short duration (12 weeks) of uncertain generalizability with only the first 75% of the randomized data made available. Since it was a well-tolerated oral medication and because it is added on to a C5 inhibitor, which obviates the concerns for breakthrough hemolysis and thrombosis as with iptacopan or pegcetacoplan monotherapy, we rate danicopan added on to a C5 inhibitor for the treatment of PNH patients with clinically significant EVH as comparable or better than a C5 inhibitor alone (C++).

Iptacopan and Add-On Danicopan Versus Pegcetacoplan

For treatment-experienced PNH patients with clinically significant EVH, clinical experts and patients would consider switching to pegcetacoplan. However, there were no studies that compared iptacopan or add-on danicopan to pegcetacoplan to evaluate the comparative clinical efficacy of these options. And due to differences across trials, no quantitative indirect comparisons could be conducted. Qualitatively, although these proximal complement inhibitors target different molecules and the severity of PNH among participants differed across trials, they seem to share a common hematologic response in reducing hemolysis, blood transfusions, and fatigue and improving hemoglobin. One major advantage for danicopan is that it is added on to a C5 inhibitor, which obviates the concerns for breakthrough hemolysis and thrombosis that can happen with pegcetacoplan monotherapy. Thus, patients and clinicians may prefer add-on danicopan to a C5 inhibitor than pegcetacoplan based on the balance of benefits and harms. Although not added on to a C5 inhibitor, patients may prefer the more convenient oral option of iptacopan to pegcetacoplan which requires a cumbersome subcutaneously administration twice weekly. In summary, there is still considerable uncertainty about the comparative net health benefits of iptacopan versus pegcetacoplan and danicopan add-on versus pegcetacoplan. As such, we rated these comparisons as insufficient (I).

Table 3.5. Evidence Ratings

Population	Treatment	Comparator	Evidence Rating
Treatment-Naïve to Complement Inhibitors	Iptacopan	C5 Inhibitor	I: Insufficient
Treatment-Experienced on a Stable C5 Inhibitor Regimen with Clinically Significant EVH	Iptacopan	C5 Inhibitor	P/I: Promising but Inconclusive
	Iptacopan	Pegcetacoplan	I: Insufficient
	Danicopan + C5 Inhibitors	C5 Inhibitor	C++: Comparable or better
	Danicopan + C5 Inhibitors	Pegcetacoplan	I: Insufficient

CTAF Votes

Table 3.6. CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
***Patient Population**: Treatment-naïve PNH patients*		
Is the currently available evidence adequate to demonstrate that the net health benefit of iptacopan is superior to that provided by C5 inhibitor therapies (eculizumab, ravulizumab)?	1	12
***Patient Population**: Treatment-experienced on a stable C5 Inhibitor regimen with clinically significant extravascular hemolysis*		
Is the currently available evidence adequate to demonstrate that the net health benefit of switching to iptacopan is superior to that provided by continuing a C5 inhibitor?	6	7
Is the currently available evidence adequate to demonstrate that the net health of switching to iptacopan is superior to that provided by switching to pegcetacoplan?	1	12
Is the currently available evidence adequate to demonstrate that the net health benefit of adding danicopan to a C5 inhibitor is superior to that provided by continuing a C5 inhibitor alone?	10	3
Is the currently available evidence adequate to demonstrate that the net health benefit of adding danicopan to a C5 inhibitor is superior to that provided by switching to pegcetacoplan?	0	13

A great majority of the panel voted that the evidence is not adequate to demonstrate that the net health benefit of iptacopan is superior to that provided by C5 inhibitor therapies in treatment -naive PNH patients. The panel members emphasized the lack of a comparison arm in the trials and that the data was insufficient.

By a one-vote majority, the panel voted that the evidence is not adequate to demonstrate that the net health benefit of switching to iptacopan is superior to continuing C5 inhibitor therapy in treatment-experienced PNH patients on a stable C5 Inhibitor regimen with clinically significant extravascular hemolysis. Many panel members expressed concerns about breakthrough hemolysis, the one case of death presented in the trials due to an encapsulated organism, and uncertainty about the long-term safety of iptacopan. While clinical experts believe iptacopan would provide benefits for treatment-experienced PNH patients who have persistent clinically significant extravascular hemolysis, they also spoke about how some patients could be non-compliant and how missing a dose can result in potentially life-threatening outcomes, including breakthrough hemolysis and, thus, expressed uncertainty about real-world outcomes.

The great majority of the panel voted that the evidence is not adequate to demonstrate that the net health benefit of switching to iptacopan is superior to switching to pegcetacoplan. Panel members raised concerns about the lack of head-to-head comparisons, although they noted both options provided a good hematologic response, i.e., hemoglobin improvement and transfusion reduction.

The majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of adding danicopan to a C5 inhibitor is superior to that provided by continuing a C5 inhibitor alone in treatment-experienced PNH patients with clinically significant extravascular

hemolysis. While the panel heard about the benefits of danicopan, such as improved hematologic response, transfusion avoidance, and improved fatigue without concerns of breakthrough hemolysis and thrombosis because of the added C5 inhibitors, they spoke about limitations in the evidence, such as the short duration of trials and small population. Other panel members raised concerns about long-term safety, given the dual blockage of the proximal and terminal complement pathways. The clinical experts spoke about the lack of long-term data but said the initial safety data were re-assuring and were hopeful for more long-term safety information as it becomes available.

The panel unanimously voted that the currently available evidence is not adequate to demonstrate that the net health benefit of adding danicopan to a C5 inhibitor is superior to that provided by switching to pegcetacoplan. Panel members expressed concerns about the lack of head-to-head data.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. The model time-horizon was five years, and costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of treatment-experienced patients with PNH with clinically significant extravascular hemolysis being treated with: 1) iptacopan or ravulizumab, and 2) add-on danicopan to ravulizumab or ravulizumab alone. Each intervention (iptacopan and add-on danicopan) was compared independently to ravulizumab alone using relevant clinical trial data. The model cycle length was 24 weeks, based on the rationale observed in prior published economic models and clinical data.[1,2] While iptacopan was a potential treatment option for the treatment naïve population, we did not model the cost-effectiveness of iptacopan in this population because we did not have any comparative data to inform an analysis of iptacopan versus other treatments. The clinical study that assessed iptacopan in a treatment naïve population (APPOINT-PNH) was a single-armed trial.

The Markov model structure consisted of four health states, including two for transfusion avoidant, one for transfusion dependent, and death (Figure 4.1). The two transfusion avoidant states were differentiated between "Hemoglobin normalized" and "Hemoglobin not normalized". These two hemoglobin (Hgb) states were based on whether patients were able to attain normalized levels (i.e., above the lower limit or normal range) during each drug's respective clinical trial period. For iptacopan this was 24 weeks, and for danicopan, 12 weeks. Additionally, trials used different thresholds for the definition of Hgb normalized with a range from 10.5 to 12 g/dL. As we did not have individual patient level data to use a single common threshold for Hgb normalization, we were limited to using trial-specific thresholds. Patients remained in the model until the end of the time horizon or death. All patients could transition to death from all causes from any of the alive health states. In addition, patients could die from experiencing thrombotic events.

Figure 4.1. Model Structure

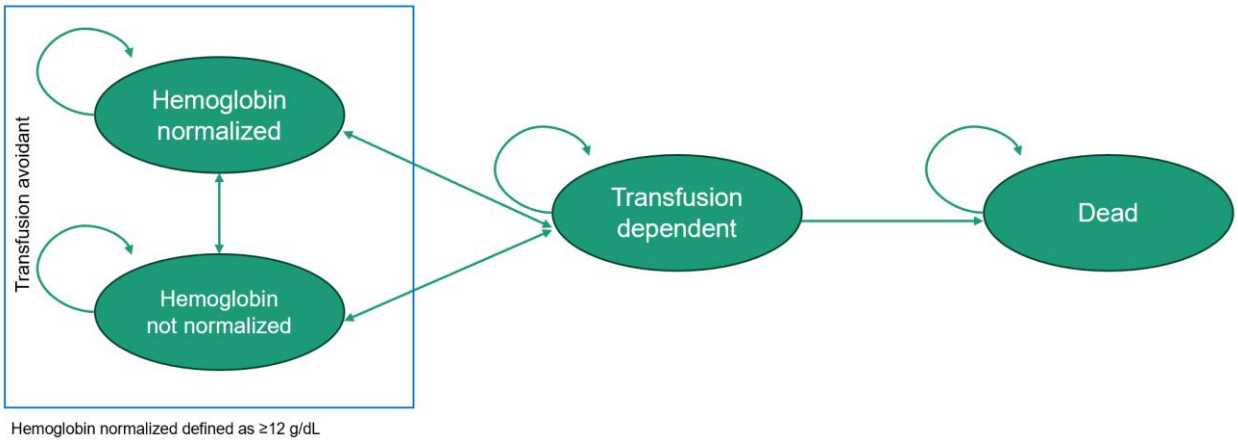


Figure adapted from Fishman et al. 2023[45]

In response to public comments, updated clinical trial results, and drug price availability, changes to the economic evaluation between the draft Evidence Report and the revised Evidence Report included:

- We used the publicly available wholesale acquisition cost ($45205.48 for 60 capsules) for iptacopan that translates to an annual cost of $550,377.[46] Our draft Evidence Report was completed prior to iptacopan's FDA approval and used a placeholder price of $485,000 annually.[46]
- The BTH probability for iptacopan changed from 3.23% to 4.96% based on recently presented findings at a scientific congress[30]
- The MAVE probability for iptacopan changed from 1.61% to 1.63% based on recently presented findings at a scientific congress[30]
- In the previous report, we used a BTH probability of 17.14% for ravulizumab from the APPLY trial. However, the C5 inhibitor arm from the APPLY trial consisted mainly of eculizumab patients, which has shown to have higher BTH rates than ravulizumab. Therefore, we used a weighted average of patients treated with ravulizumab experiencing BTH from Study 301 and 302, which was calculated to be 2.25%.[47,48] The estimate of 17.14% was used in a scenario analysis and did not alter our conclusion regarding the cost-effectiveness of iptacopan.

Changes to the economic evaluation between the revised Evidence Report and the final Evidence Report included:

- In the revised Evidence Report, we programmed the cost-offset cap scenario by fixing the price of ravulizuamb so that the total cost-offsets for iptacopan did not exceed $150,000 for

any year during the 5-year time horizon. In taking this approach, the full $150,000 cost-offset was not realized each year. We modified our approach to calculate the excess cost-offsets at a cycle level and then aggregated these costs to an annual level to ensure that iptacopan received the full $150,000 cost-offset credit during each year of the time horizon.

4.2. Key Model Assumptions and Inputs

Our model included several assumptions stated in Table 4.1.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Utility values were consistent across definitions of hemoglobin normalization.	In the absence of utility data from manufacturers, we relied on publicly available data and the utility values for patients achieving hemoglobin normalization.
Patients remained in their initial health state for the duration of the five-year time horizon.	There was a lack of data on long-term outcomes for iptacopan and danicopan to inform a lifetime horizon. Further, incremental mortality effects are minimal.
The assumptions for treatment efficacy hold after primary endpoint of the trials.	There was a lack of patient-level data to inform transitions after the first cycle so we assumed the initial treatment effect at 12 and 24 weeks for danicopan and iptacopan, respectively, held throughout the model time horizon.
Ravulizumab was equivalent to eculizumab with respect to efficacy.	The control arm for the clinical trials of iptacopan and danicopan consisted of a mix of ravulizumab and eculizumab. We applied the efficacy outcomes to only ravulizumab in our model since 1) we do not have patient-level data to inform treatment-specific efficacy, 2) we heard from clinical experts that ravulizumab is the preferred treatment choice over eculizumab based on treatment regimen, and 3) ravulizumab has been shown to be non-inferior to eculizumab.[47]

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Iptacopan
- Danicopan added to ravulizumab

Comparators

The comparators for these interventions were ravulizumab in the treatment-experienced with clinically significant EVH population.

Clinical Inputs

We used interim results from the APPLY-PNH trial for iptacopan in the treatment-experienced with clinically significant EVH population. We used interim results from the ALPHA trial for danicopan added to a C5 inhibitor in the treatment-experienced with clinically significant EVH population.

Transition Probabilities

Using the proposed model structure and the follow-up periods for the clinical trials of iptacopan (24 weeks) and danicopan (12 weeks), we modeled the first cycle (24 weeks) using limited publicly available clinical trial data (Tables 4.2 and 4.3). In the absence of additional data to inform transition probabilities for all subsequent model cycles, we assumed patients stayed in their first cycle state for the remainder of the five-year model time horizon.

Table 4.2. Transition Probabilities for Iptacopan Versus Ravulizumab in Treatment-Experienced With Clinically Significant EVH Population

	Iptacopan First Model Cycle (24 weeks)	Ravulizumab First Model Cycle (24 weeks)	Subsequent Model Cycles
Transfusion Avoidant and Hgb Normalized	0.688	0.018	NA
Transfusion Avoidant and Hgb Not Normalized	0.276	0.243	NA
Transfusion Dependent	0.036	0.739	NA
Reference	APPLY-PNH (96.4% of participants achieved transfusion avoidance, 68.8% of whom had normalized hemoglobin) [41]	APPLY-PNH (26.1% of participants achieved transfusion avoidance, 1.8% of whom had normalized hemoglobin) [41]	NA

Hgb: hemoglobin, NA: not available

Table 4.3. Transition Probabilities for Danicopan and Ravulizumab Versus Ravulizumab Alone in Treatment-Experienced With Clinically Significant EVH Population

	Danicopan Plus Ravulizumab First Model Cycle (12 weeks)*	Ravulizumab First Model Cycle (12 weeks)*	Subsequent Model Cycles
Transfusion Avoidant and Hgb Normalized	0.286	0.0	NA
Transfusion Avoidant and Hgb Not Normalized	0.547	0.381	NA
Transfusion Dependent	0.167	0.619	NA
Reference	ALPHA (83.3% of participants achieved transfusion avoidance, 28.6% of whom had normalized hemoglobin) [35]	ALPHA (38.1% of participants achieved transfusion avoidance, none of whom had normalized hemoglobin) [35]	NA

*Interim ALPHA trial results were at 12 weeks but applied and assumed as 24 weeks in the model
Hgb: hemoglobin, NA: not available

Mortality

Data on the direct mortality effects of iptacopan and danicopan were not available. From the scoping phase with clinical experts, one of the leading causes of mortality in PNH patients is from major adverse vascular events (MAVE), most notably from thrombosis. A mortality effect through MAVE was modeled based on an input from the literature (Table 4.4).

Table 4.4. Mortality Inputs

Parameter	Value	Source
Mortality associated with MAVE occurrence	RR of 13.9%	Jang et al. 2016[49]
All-Cause Mortality		U.S. Life Tables

MAVE: major adverse vascular event

Adverse Events

The Aes we included in our model are breakthrough hemolysis (BTH) and MAVE, using data from the clinical trials, as detailed in Table 4.5. The associated disutilities and costs associated with these Aes are detailed in Table 4.6.

Table 4.5. Adverse Events in Treatment Experienced With Clinically Significant EVH Population

Parameter	Iptacopan	Ravulizumab (Iptacopan Comparison)	Danicopan Plus C5 Inhibitor	Ravulizumab (Danicopan Comparison)
Breakthrough Hemolysis, %	4.96	2.25	4.0	0*
Major Adverse Vascular Events, %	1.63	0	0†	0*

NA: not available

*Based on Study 302[47]

†Assumption based on Study 302[47]

Table 4.6. Disutilities and Costs Associated with Adverse Events

Parameter	Disutility	Cost
Breakthrough Hemolysis	-0.0006[15]; assumed to last one model cycle (24 weeks)	$12,360 [50]
Major Adverse Vascular Events	-0.0006[51]; assumed to last one model cycle (24 weeks)	$25,674 [52]

Health State Utilities

Health state utilities were derived from publicly available literature, and manufacturer submitted data and applied to health states. We used consistent health state utility values across treatments evaluated in the model.

We used utility values derived from the PRINCE trial that assessed pegcetacoplan compared to eculizumab (Table 4.7).[45] From PRINCE, the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) data were used to map to EQ-5D-3L utility weights using an algorithm.[53] When the PNH health state utilities were higher than the general population utilities at the same age, we adjusted the PNH-specific utilities by applying the same relative decrease in utility that was seen by age in the general population.[54] Further detail on the utility values used and the rationale can be found in the Supplementary Materials Section E2.

Table 4.7. Health State Utilities in Treatment Experienced With Clinically Significant EVH Population

Parameter	Value	Source
General population	Age-adjusted	Jiang et al. 2021[54]
Hgb normalized	0.869	Fishman et al. 2023 [45]
Hgb not normalized	0.820	
Transfusion required	0.818	

Hgb: hemoglobin

Cost Inputs

All costs used in the model were updated to 2023 dollars.

Drug Costs

Details on drug utilization to estimate costs can be found in the Supplemental Materials Section E2. For ravulizumab, we obtained the annual net price from the Centers for Medicare & Medicaid Services average sales price (ASP) drug pricing file that is updated quarterly.[55] The price from this file is inclusive of the ASP and the associated mark-up (6%). For Ravulizumab, which used weight-based dosing, we assumed a mean body weight of 69 kg based on clinical trial data.[34] Details regarding drug costs are included in Table 4.8.

For iptacopan, we used a cost per dose of $753 based on recently available wholesale acquisition costs from REDBOOK.[46]. For danicopan, a placeholder price of $150,000 was used given that the net price is not yet available. This estimate was from IPD analytics.[56] Details regarding drug costs are included in Table 4.8, and Additionally, non-drug costs related to PNH are detailed in the Supplementary Materials Table E2.2.

Table 4.8 Drug Costs

Drug	Acquisition Cost per Dose	Acquisition Cost per Year
Iptacopan	$753	$550,377
Danicopan*	$137	$150,000
Ravulizumab (Ultomiris®)**†	Loading Dose: $56,260 Maintenance Dose: $68,762	Year 1: $518,325 Year 2: $476,762

* Placeholder price based on IPD Analytics[56]

**Acquisition price does not include mark-up and is based on a price of $208.37 per 10mg (+ 6%; $13.30).[55]

†Assuming a mean body weight of 69 kg (Lee et al 2019), loading dose (2700mg), maintenance dose (3300mg) every 8 weeks starting 2 weeks after loading dose.

4.3. Model Outcomes

Model outcomes included total life years (Lys) gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and total costs for each intervention over a five-year time horizon. Total costs, LY's, QALYs, and evLYs gained were reported as discounted values, using a discount rate of 3% per annum.

4.4. Results

Base-Case Results

The total discounted costs, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and life years (Lys) gained are detailed in Table 4.9 for iptacopan compared to ravulizumab and in Table 4.10 for add-on danicopan to ravulizumab compared to ravulizumab alone for treatment-experienced PNH patients with clinically significant EVH. Over the five-year time horizon at the annual price of $550,377, treatment with iptacopan resulted in higher incremental costs of approximately $$200,000 and incremental gains in QALYs and evLYs of approximately 0.15 and 0.15, respectively, compared to ravulizumab from the health care sector perspective. Life years were fractionally lower for iptacopan as 1.63% of patients experienced MAVE compared to 0% of patients treated with ravulizumab; however, as the difference was minimal and less than 0.01, we assumed equivalence. As a result, the evLYs were the same as QALYs for iptacopan as there was no survival benefit associated with the intervention. The resultant incremental cost-effectiveness ratios are presented in Table 4.11.

At the annual placeholder price of $150,000, treatment with add-on danicopan resulted in high incremental costs of approximately $593,000 and incremental gains in QALYs and evLYs of approximately 0.06 and 0.06, respectively, compared to ravulizumab over a five-year time horizon. Life years were the same across both treatment regimens as there were no differences in MAVE experienced. The evLYs were the same as QALYs for add-on danicopan as there was no survival benefit associated with the intervention.

The differences in outcomes for ravulizumab across both comparisons were due to the slightly older mean age in the ALPHA trial, different transition probabilities assumed for the first cycle, and differences in BTH rates used.

Table 4.9. Results for the Base-Case for Iptacopan Compared to Ravulizumab

Treatment	Drug Cost	Total Cost	QALYs	Life Years	evLYs
Iptacopan	$2,360,000	$2,375,000	3.65	4.29	3.65
Ravulizumab	$2,088,000	$2,175,000	3.50	4.29	3.50

Table 4.10. Results for the Base-Case for add-on Danicopan Compared to Ravulizumab Alone

Treatment	Drug Cost*	Total Cost*	QALYs	Life Years	evLYs
Danicopan + Ravulizumab	$2,712,000*	$2,737,000	3.51	4.26	3.51
Ravulizumab	$2,073,000	$2,144,000	3.45	4.26	3.45

*Based on placeholder price

Table 4.11. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained*	Cost per evLY Gained
Iptacopan	Ravulizumab	$1,368,000	--†	$1,368,000
Danicopan + Ravulizumab	Ravulizumab	$9,457,000*	--±	$9,457,000*

*Based on placeholder price

†Not calculable due to assumed equivalence in life-years (difference of <0.01)

±Not calculable due to equivalence in life-years

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Notably, the most influential inputs on the findings for iptacopan were the drug prices and utility values used, and the varied drug prices had an impact on the interpretation of the cost-effectiveness. For add-on danicopan, the most influential inputs were the utility and clinical efficacy inputs but the interpretation of the cost-effectiveness did not change. Detailed results from the one-way sensitivity analysis for iptacopan and add-on danicopan can be found in Supplement Section E3.

Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1000 simulations, then calculating the proportion of simulations that were cost-effective at various commonly used willingness-to-pay thresholds. The results are shown in Tables 4.12. and 4.13.

Table 4.12. Probabilistic Sensitivity Analysis Cost per QALY Gained Results

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Iptacopan	13.10%	13.80%	15.60%	16.20%
Add-on Danicopan*	0.00%	0.00%	0.00%	0.00%

*based on placeholder price

Table 4.13. Probabilistic Sensitivity Analysis Cost per evLY Gained Results

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Iptacopan	13.10%	13.80%	15.60%	16.20%
Add-on Danicopan*	0.00%	0.00%	0.00%	0.00%

*based on placeholder price

Scenario Analyses

We conducted scenario analyses to examine uncertainty and potential variation in the findings. The scenarios are presented below and the findings are presented in Table E4.1 and E4.2.

1. Modified societal perspective
2. Lifetime time horizon
3. Utility values from prior economic models using PEGASUS data
4. A BTH rate of 17.14% for ravulizumab in the assessment of iptacopan given the rate seen in the APPLY trial for the C5 inhibitor arm, which included ravulizumab and eculizumab
5. A cost-offset cap model in which the health system cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment.

Threshold Analyses

Threshold analyses were conducted to calculate the price needed to meet commonly accepted cost-effectiveness thresholds for QALY and evLY gained (Table 4.12). The results were the same for both as there were no survival benefits associated with either iptacopan or add-on danicopan. We also included threshold prices based on the $150,000 cost-offset scenario mentioned above in Table 4.15. This scenario was not applied to the add-on danicopan comparison to ravulizumab alone as the cost-offsets never exceeded $150,000 annually.

Table 4.14. QALY and evLYG-Based Threshold Analysis Results

	Annual Price to Achieve $50,000 per QALY and evLY Gained	Annual Price to Achieve $100,000 per QALY and evLY Gained	Annual Price to Achieve $150,000 per QALY and evLY Gained	Annual Price to Achieve $200,000 per QALY and evLY Gained
Iptacopan	$505,000	$507,000	$509,000	$511,000
Add-on Danicopan	$11,600	$12,300	$13,100	$13,800

*evLYG: equal-value life year, QALY: quality-adjusted life-year

Table 4.15. QALY and evLYG-Based Threshold Analysis Results Based on the Annual $150,000 Cost-offset Cap Scenario

	Annual Price to Achieve $50,000 per QALY and evLY Gained	Annual Price to Achieve $100,000 per QALY and evLY Gained	Annual Price to Achieve $150,000 per QALY and evLY Gained	Annual Price to Achieve $200,000 per QALY and evLY Gained
Iptacopan	$177,000	$178,000	$180,000	$182,000

*evLYG: equal-value life year, QALY: quality-adjusted life-year

Prior Economic Models

Prior models for treatments in PNH have used various modeling schematics.[15,45,57-59] The schematic that we chose was informed from models used to assess pegcetacoplan, which we did not include in our model.[45,57] Models used to assess ravulizumab and eculizumab, used a modeling approach that included BTH as the primary driver of health state transitions and with prior BTH impacting the probability of future BTH.[15,58] However, in our scoping phase with clinical experts, BTH was considered more of an adverse event, rather than being the mechanism of PNH prognosis. Additionally, there was not a strong feeling that a history of experiencing BTH would increase the likelihood of experiencing another BTH episode. It is difficult to compare our base-case results to prior models as we did not have data to inform transition probabilities beyond the first cycle. Based on our scenario analysis of a lifetime time horizon, compared to prior models, we saw similarities in total costs and QALYs, as well as drug costs accounting for the vast majority of total costs. Additionally, a recent model presented at a scientific congress assessed iptacopan compared to C5 inhibitors.[60] This study was only available in abstract form and as such, details such as model inputs and the schematic were not available for a fair comparison of base-case results. The one result that was comparable was patient time loss due to treatment with ravulizumab where the study estimated 730 hours lost and we estimated a similar 803 hours lost from a lifetime horizon.

Uncertainty and Controversies

Given the limited amount of publicly available data to inform our cost-effectiveness analysis, we were reduced to estimating the initial cycle (24 weeks) based on clinical trial data since we did not receive data from manufacturers that would inform transitions between health states after 24 weeks. We assumed patients stayed in their initial health states until the end of the model. Additionally, the clinical data that we used to inform model parameters had limitations such as small sample sizes and short follow-up periods (24 weeks for iptacopan and 12 weeks for danicopan). Studies with longer follow-up periods would better inform our model parameters.

An additional limitation we faced being constrained to available data was the appropriate rate to use for BTH in the comparison of iptacopan and ravulizumab. In the APPLY trial, the BTH rate of 17.14% seen for the C5i arm, composed of patients on ravulizumab and eculizumab, was likely

skewed by including both extravascular and intravascular hemolysis. This is in stark contrast to the 4% and 0% intravascular BTH that was seen in Study 301 and 302, respectively for ravulizumab. [47,48] We felt the evidence for BTH was stronger from Studies 301 and 302 for ravulizumab, so we used a weighted average of 2.25% and used the 17.14% as a scenario analysis. However, using the 17.14% for ravulizumab BTH in the iptacopan assessment as a scenario analysis did not change our conclusion.

Our threshold analysis results for iptacopan highlighted an area of concern. With iptacopan, because the baseline for comparison is ravulizumab, which is already an extremely costly treatment at ~$477,000, any incremental gains for iptacopan would lead to an even higher value-based price. As expected, our calculated threshold prices for iptacopan were higher than the price of ravulizumab, with an annual price of $507,000 to $509,000. We calculated that approximately 97% of the annual threshold price of iptacopan were attributable to cost-offsets, the majority of which were driven by comparator drug cost-offsets. This questions whether a new drug for PNH with a high price and marginal QALY gains can ever be cost-effective since the standard of care treatment (C5 inhibitors) is not known to meet common cost-effectiveness thresholds. Prior models have found ravulizumab to be "cost-effective"; however, the comparator was eculizumab, which in its comparison to standard care was not cost-effective at an incremental cost per QALY gained of $2.270 million after converting to 2023 USD.[59] In accordance with ICER's methods (see page 11, section 5), we tried to address this concern by including a cost-offset cap model scenario in which the health system cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment.

4.5. Summary and Comment

In our five-year time horizon model, when treatment-experienced PNH patients with clinically significant EVH were treated with either iptacopan or add-on danicopan, patients had small or no gains in QALYs, evLYs, and life years compared to their respective treatment arm of ravulizumab. As previously mentioned, our model was limited to an initial cycle transition due to a lack of available data. Our analysis suggests that iptacopan would far exceed commonly used thresholds at an annual price of $550,377. Furthermore, the estimated traditional threshold findings for iptacopan are primarily driven by the comparator drug cost-offsets. Finally, at the placeholder price of $150,000 add-on danicopan did not meet commonly accepted cost-effectiveness thresholds.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	Thrombosis is the main cause of permanent disability and death and is largely mitigated by existing C5 inhibitor therapies. Newer therapies seem promising but have uncertain protection against thrombosis given small-sized trials of short duration.
Magnitude of the lifetime impact on individual patients of the condition being treated	PNH is a lifelong disorder beginning at a median age in the 30s. With C5 inhibitor therapy most patients have controlled disease, but 20-30% have more illness burden due to EVH.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Less fatigue and fewer blood transfusions can enhance patients' ability to achieve major life goals.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	While PNH does not typically require significant caregiver assistance, improvement in fatigue can reduce relationship strain.
Patients' ability to manage and sustain treatment given the complexity of regimen	C5 inhibitors are administered intravenously every two or eight weeks depending on the type. Pegcetacoplan requires an on-body twice-weekly subcutaneous administration that is burdensome. Thus, oral iptacopan is more convenient, but is more susceptible to breakthrough hemolysis which can occur with even just a few missed doses. While Danicopan is also oral, patients need to also continue C5 inhibitor infusions.
Society's goal of reducing health inequities	Iptacopan and add-on danicopan would provide more treatment options. However, potential reduction in health inequities may be tempered by high out-of-pocket costs among underinsured individuals, who are more likely to be racial/ethnic minorities.

CTAF Votes

At the public meeting, the CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective new treatment for PNH, on the basis of the following contextual considerations:

Table 5.3. CTAF Votes on Contextual Considerations Questions

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	0	5	6	2	0
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	6	7	0

The panel vote on acuity of need was split across low, average, and high priority. Five panel members voted "low" priority, six panel members voted "average" priority, and two panel members voted for "high priority." Panelists who voted "low" or "average" noted that thrombosis, which is the main cause of permanent disability and death, is largely mitigated by the existing standard of care (C5 inhibitor therapies).

By a majority of one vote, the panel voted that given the magnitude of the lifetime impact on individual patients, high priority should be given to any treatment. Patient and clinical experts expressed the struggles with the unpredictability of PNH and how it affects patients for the rest of their lives. Considering the various areas of life that PNH affects, patient experts also expressed that they were willing to take any form of treatment despite the unknown risks of the treatment.

What are the relative effects of switching to iptacopan versus continuing C5 inhibitors on the following outcomes that inform judgment of the overall long-term value for money of iptacopan?

Table 5.4. CTAF Votes on Potential Other Benefits or Disadvantages Questions

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	8	5
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	3	9	1
Patients' ability to manage and sustain treatment given the complexity of regimen	1	0	2	7	3
Society's goal of reducing health inequities	1	2	8	2	0

Eight panel members voted that switching to iptacopan versus continuing C5 inhibitors would have a minor positive effect on patients' ability to achieve major life goals related to education, work, or family life, while five panel members voted on a major positive effect. The panel heard from clinical and patient experts who shared that achieving transfusion independence is a transformative change to patients, as it would positively affect their time and commitment to treatment administration.

A majority of the panel voted that switching to iptacopan would have a minor positive effect on caregivers' quality of life and/or ability to achieve major life goals. Panel members considered the impact of PNH on family and spouses' commitment to assisting patients with doctor appointments and managing symptoms, as shared by clinical experts and oral commenters.

There were seven votes that switching to iptacopan would have a minor positive effect on patients' ability to manage and sustain treatment given the complexity of regimen. The clinical and patient experts expressed that sustaining treatment depends heavily on the patients' ability to adhere to a complex regimen. Although the patient expert expressed that there would be a positive emotional change to no longer visit an infusion center for administration, the case is individualized for each patient.

Eight panel members voted that switching to iptacopan would have no difference on society's goal of reducing health inequities, while one voted for major negative effect, two for minor negative effect, and two for minor positive effect. The panel members considered how there are no major racial or ethnic differences in the prevalence of PNH, but there may be disparities between rural and urban areas and access to clinics.

What are the relative effects of adding danicopan to C5 inhibitors versus C5 inhibitors alone on the following outcomes that inform judgment of the overall long-term value for money of danicopan?

CTAF Votes on Potential Other Benefits or Disadvantages Questions

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	3	9	1
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	7	6	0
Patients' ability to manage and sustain treatment given the complexity of regimen	1	7	2	3	0
Society's goal of reducing health inequities	2	2	9	0	0

The panel voted with similar discussions to the previous voting questions for iptacopan but in the context of danicopan. Nine panel members voted that adding danicopan to C5 inhibitors would have a minor positive effect on patients' ability to achieve major life goals related to education, work, or family life. Three panel members voted for no difference, while one panel member voted for major positive effect. A majority by one vote agreed that adding danicopan to C5 inhibitors would have no difference on caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life. Seven panel members voted that adding danicopan to C5 inhibitors would have a minor negative effect on patients' ability to manage and sustain treatment given the complexity of the regimen of adding an oral drug while continuing C5 inhibitor infusions, one panelist voted that this will have a major negative effect, while two voted for no difference. With nine votes, a majority of the panel voted that adding danicopan would have no difference on society's goal of reducing health inequities, while two voted for major negative effect and two for minor negative effect.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the intervention(s) are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained.

ICER's methods include analyses that examine the potential for "shared savings" of cost offsets from a new therapy in situations where a large percentage of the traditional HBPB comes from reductions in use or elimination of therapies that themselves have prices that are not believed to be aligned with benefits to patients. These methods have most commonly been employed when the new treatment is a single- or short-term use treatment such as a cell or gene therapy, but the approach is also relevant when considering the cost-effectiveness of chronic therapies.

When all cost offsets are assigned to the intervention, the HBPB for iptacopan could be as high as $507,000 to $509,000 annually. However, we calculated that approximately 97% of the HBPB for iptacopan using the traditional approach comes from offsetting the cost of the comparator drug, a C5 inhibitor ravulizumab. The existing C5 inhibitor therapies (39 eculizumab and ravulizumab) are extremely costly, at approximately $450,000 to $500,000 per year. Although prior models have found ravulizumab to be "cost-effective," the comparator in those models was eculizumab, which when compared to standard of care did not meet commonly accepted cost-effectiveness thresholds (incremental cost per QALY gained of $2.27 million after converting to 2023 USD). If prices of C5 inhibitors were to come down from effective competition or other measures, the appropriate pricing of new treatments such as iptacopan, as suggested by cost effectiveness analysis, would need to come down as well.

Given that ipatacopan met the criteria of having a large percentage of its HBPB come from cost offsets of C5 inhibitor therapies that, themselves, have prices that are not believed to be aligned with benefits to patients, ICER used a shared savings scenario with a $150,000 annual cap on cost offsets to estimate what we feel is the most appropriate HBPB. The HBPB for iptacopan, using this shared savings analysis, is $178,000 to $180,000 annually.

The HBPB for danicopan used as add-on therapy to a C5 inhibitor, which was not subject to any shared savings scenario, is an annual price of $12,300 to $13,100.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Iptacopan and Add-on Danicopan

Annual Prices Based on QALYs or evLYs Gained	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Iptacopan				
QALYs & evLYs Gained*	$550,377	$178,000	$180,000	67.30%-67.61%
Add-on Danicopan				
QALYs & evLYs Gained*	Not available	$12,300	$13,100	Not available

*Threshold prices based on QALYs or evLYs gained were equivalent as there was no life extension associated with either treatment

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

CTAF Votes

Table 6.2. CTAF Votes on Long-Term Value for Money at Current Prices

Question	Low long-term value for money at current pricing	Intermediate long-term value for money at current pricing	High long-term value for money at current pricing
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with iptacopan versus C5 inhibitors?	12	1	0
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with danicopan added to C5 inhibitors versus C5 inhibitors alone?*			

The majority of the panel voted that iptacopan, at its current price of about $550,377, provides a "low" long-term value for money. Many panel members expressed concern about the cost of the current standard of care, with many concluding that too much of the value of iptacopan reflected offsetting the cost of overpriced C5 inhibitors. They also expressed caution about affordability and continuing to build on an already over-priced system. One panel member voted for "intermediate" long-term value, noting the contextual considerations and the benefit iptacopan will provide for patients with clinically significant extravascular hemolysis versus the highly-priced C5 inhibitors.

*Long-term value for money votes were not taken at the public meeting because a net price for danicopan was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of iptacopan and danicopan for patients with PNH. We used the current annual WAC price for iptacopan ($550,377), a placeholder price for danicopan ($150,000 annually) and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each drug in our estimates of budget impact.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with iptacopan and danicopan. In alignment with the cost-effectiveness analysis, the eligible population for iptacopan and danicopan is for treatment-experienced patients with PNH with clinically significant extravascular hemolysis. To estimate the size of the potential candidate population we used inputs for the US population size (344,207,840),[61] the prevalence of PNH (12.5 cases per 1,000,000; 0.0000125%),[62] the percentage of patients with PNH who are symptomatic and eligible for a C5i (61.3%, assuming that the percentage of patients who are symptomatic are those with a history of RBC transfusions),[6] and the percentage of patients (21%) that are not controlled on current therapy (i.e., experience a clinically significant extravascular hemolysis and would be eligible to switch to iptacopan or danicopan as an add-on therapy).[63] Applying these sources results in estimates of 554 treatment experienced patients in the US over five years. Given we are assessing two new market entrants for the prevalent population, we assumed that 50% of patients each year will initiate iptacopan and the remaining 50% of patients will initiate danicopan (added on to standard of care, i.e., ravulizumab). We recognize that there may be differential uptake between iptacopan and danicopan in practice. Our objective is intended to provide a framework in which decision-makers and policymakers can then apply their own assumptions that align with their context. Applying these sources results in estimates of 277 eligible patients in the US for iptacopan, and 277 eligible patients in the US for danicopan. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 55 patients per year for iptacopan and 55 patients per year for danicopan. Our analysis is focused on patients who are treatment experienced and, consequently, represents an underestimate of the potentially eligible patient population if iptacopan is used for patients who are treatment naïve.

7.2. Results

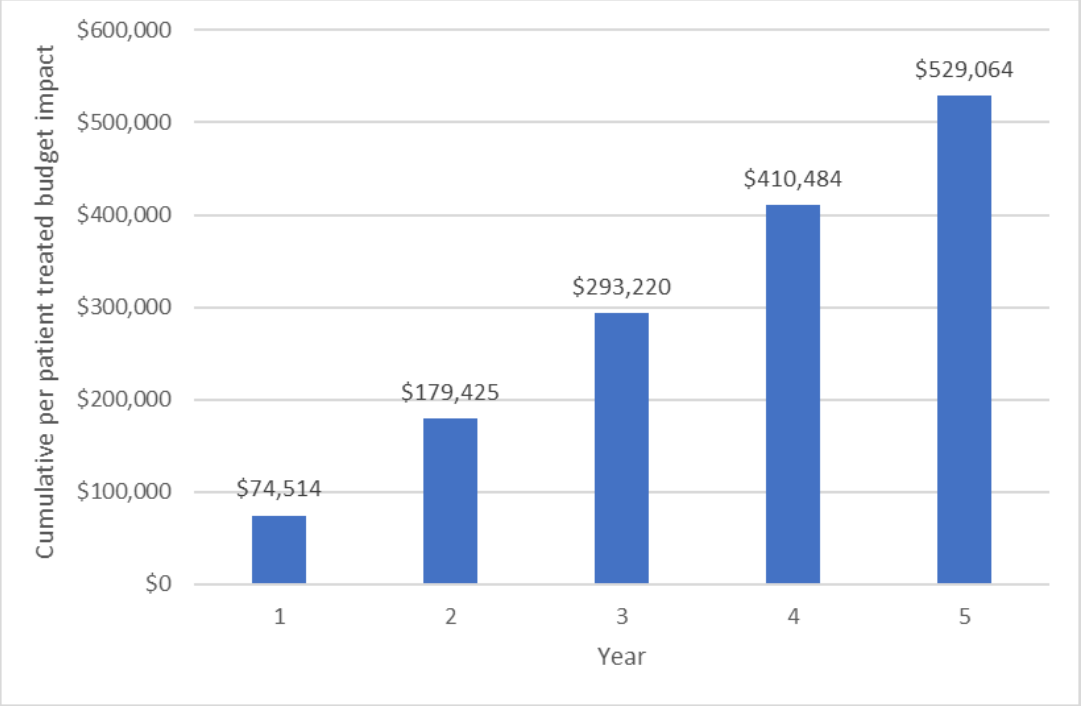
Results showed that at the current annual WAC price for iptacopan ($550,377) and the placeholder price for danicopan ($150,000 annually), all patients (N=55 patients per year) could be treated over the span of five years without crossing the ICER budget impact threshold of $735 million per year. Given that the data used to inform our estimate of the percentage of patients with PNH who are symptomatic and eligible for a C5i (61.3%) is likely an underestimate, if we assume that 100% of patients diagnosed with PNH are eligible for a C5i, all patients (N=90 patients per year) could still be treated over the span of five years without crossing the ICER budget impact threshold.

Figure 7.1 illustrates the cumulative per patient treated budget impact for iptacopan compared to ravulizumab. There were cost-savings of -$8,049 in Year one for iptacopan compared to ravulizumab, with cumulative incremental costs increasing to $141,601 by Year five.

Figure 7.1 Cumulative Annual per Patient Treated Budget Impact for Iptacopan Compared to Ravulizumab

Figure 7.2 illustrates the cumulative per patient treated budget impact for add-on danicopan compared to danicopan alone. At the placeholder price ($150,000 annually for danicopan), the average annual budget impact per patient was $74,514 in Year one with cumulative costs increasing to $529,064 in Year five.

Figure 7.2 Cumulative Annual per Patient Treated Budget Impact for Add-On Danicopan Compared to Ravulizumab Alone at a Placeholder Price of $150,000 Annually for Danicopan



Access and Affordability Alert

ICER is not issuing an access and affordability alert for iptacopan or add-on danicopan. At iptacopan's current price of $550,377 per year and at anticipated clinical utilization levels, all patients could be treated within five years without reaching the ICER potential budget impact threshold. The price of add-on danicopan is unknown, however, at its' placeholder price and threshold prices, the ICER potential budget impact threshold was not reached at anticipated clinical utilization levels.

The purpose of an ICER access and affordability alert is to signal to stakeholders and policymakers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

8. Policy Recommendations

Following the CTAF deliberation on the evidence, a policy roundtable discussion was moderated by Dr. Steve Pearson around how best to apply the evidence on the use of iptacopan and danicopan. The policy roundtable members included two patient advocates, two clinical experts, two payers, and zero representatives from the drug maker. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

Health Equity

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective treatment options for patients with PNH are introduced in a way that will help reduce health inequities.

Safe and effective treatment for PNH should not be limited by excessive cost or other barriers to appropriate access to care. Efforts are needed to ensure that existing and new therapies for PNH, including C5 inhibitors, pegcetacoplan, iptacopan, and add-on danicopan (if approved), improve the health of patients without aggravating existing health inequities. Clinical experts and patients highlighted that the high cost of therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to new therapies prescribed, or steep out-of-pocket costs, which may be exacerbated when oral treatments are covered under the pharmaceutical benefit within an insurance plan as opposed to intravenous medications covered under the medical benefit. The cost of care is not the only factor that may contribute to health inequities. Patients and clinical experts noted that because PNH is a rare disease, hematologists with clinical expertise in the condition are often clustered in academic settings, leaving patients in underserved rural and urban areas without adequate access. Structures and policies to foster home infusion of IV therapies, travel for patients when needed, and remote collaboration between clinicians, are needed to address these barriers to appropriate care and to maximize the potential of new oral agents to reduce health inequities.

To address these concerns:

State and federal policymakers should take the following actions:

- Issue legislation to promote telehealth, such as the Creating Opportunities Now for Necessary and Effective Care Technologies (CONNECT) for Health Act of 2023 (H.R. 4189) that is being considered for Medicare beneficiaries which proposes to permanently remove all geographic restrictions that would enable the limited number of PNH specialists to advise local hematologists in regions of the country lacking this highly specialized expertise.

- Promote digital health equity through legislation, such as the Lifeline Program or the Emergency Broadband Benefit, that supports smartphone ownership and reduce broadband costs for low-income individuals.

Manufacturers should take the following actions:

- Set the price for new treatments in fair alignment with added benefits for patients.

- Provide advice and support for patients with PNH, such as assigning a case manager to help patients and families access therapies and to assist with insurance benefits navigation.

Payers should take the following actions:

- Reduce administrative burden and streamline the process to arrange for home infusion therapy for C5 inhibitors for patients who prefer this option and/or do not have easy access to an infusion center.

- When administering site of service (SOS) policies to ensure C5 inhibitors are infused in low-cost settings, patients should not be held liable for any added out-of-pocket costs and should be eligible to share in the savings realized by health plans.

- In developing coverage policies, ensure newer oral therapies have an equitable out-of-pocket cost burden under the pharmaceutical benefit compared to existing C5 inhibitors covered under the medical benefit. This is critical to make sure that the financial burden is not driving treatment choices, particularly for patients who do not live near an infusion center or cannot arrange home infusions.

Payers

Recommendation 1

Payers should be aware of several key issues regarding the treatment landscape for PNH: 1) patients and clinicians have become accustomed to and are satisfied with an intravenously administered C5 inhibitor as frontline therapy in treatment-naïve patients; 2) clinicians do not have prediction models or biomarkers to identify which patients treated with a C5 inhibitor will develop clinically significant extravascular hemolysis (cs-EVH) nor distinguish which switch or add-on proximal complement inhibitor for this population is best; and 3) there is a high value placed on individual shared decision making for patients choosing between a C5 inhibitor and non-intravenous treatment options.

Historically, payers have not employed active utilization management policies for PNH, an approach which likely reflects the limited treatment options before the availability of newer proximal complement inhibitors. Clinical experts suggested that clinicians and patients have generally expressed a 'wait-and-see' approach until longer-term evidence on the safety and effectiveness is accrued as to whether the newer monotherapy proximal complement inhibitors, including pegcetacoplan and iptacopan, will have the same durable protection against breakthrough hemolysis and thrombosis as C5 inhibitors. Given the inability to predict which patients will develop cs-EVH when treated with a C5 inhibitor or to identify which switch or add-on proximal complement inhibitor will work best for this subpopulation, both clinical experts and patient experts emphasized that patients and clinicians place a high value on shared decision-making given the important trade-offs in potential harms and benefits of the different options.

Recommendation 2

Annual coverage renewal requirements for PNH therapies should either be eliminated or implemented using a separate time-sensitive pathway to avoid missing doses, and should not penalize improvement on therapy as a reason for denial of continued coverage.

Since symptomatic and high-risk patients with PNH require indefinite therapy to prevent the untoward manifestations of the illness, coverage policies pertaining to annual renewal for existing and new PNH therapies should be designed to avoid unnecessary treatment disruptions, which patients and patient advocates expressed is an ongoing issue. Similarly, improvement in hematologic response, whether defined as hemoglobin level above a prespecified threshold or avoidance of red blood cell transfusions, should not trigger a denial of continued coverage, because withholding therapy will predictably result in hemolysis and potentially thrombosis.

Manufacturers

Recommendation 1

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of these new interventions for PNH, while there is considerable hope associated with the promise of the therapies, there also remains substantial uncertainty regarding their longer-term safety and effectiveness. Manufacturer pricing should also be moderated to reflect the substantial uncertainty about these longer-term outcomes.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Manufacturers should therefore price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty and need for indefinite therapy in PNH, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness and safety of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial benefit for patients with PNH, manufacturers should be allowed to increase pricing in accordance with benefit.

PNH treatments may also be used in other complement-mediated illnesses, such as atypical hemolytic uremic syndrome. As evidence accrues for other indications, the value of drugs should be considered across the entire portfolio of indications, and should not be priced for PNH in isolation.

Recommendation 2

Manufacturers who develop therapies for PNH as an add-on to one of their existing drugs on the market should consider reduced pricing for the add-on therapy to achieve fair value compared to monotherapy treatment options.

Because treatment for PNH is indefinite, manufacturers who develop add-on therapies for PNH should consider bundled pricing of both drugs until further evidence clarifies the value of dual therapy compared to monotherapy. This is especially pertinent to danicopan, since it is an add-on therapy to a C5 inhibitor which is very expensive and by itself not considered to be cost-effective without generic biosimilar medications available on the market.

Recommendation 3

Establish new or contribute to existing long-term registries that can be used to assess the benefits and harms of proximal complement inhibitors for the treatment of PNH.

Because the evidence based is comprised of small trials of short duration, concerns persist about uncommon but potentially serious risks of the proximal complement inhibitors, including breakthrough intravascular hemolysis and thrombosis. Whether these harms will manifest due to nonadherence or complement amplifying conditions (i.e., infections) require long-term follow-up studies that assess the durability of response and safety profiles. Registries would also enable comparative effectiveness research to identify the relative benefits and harms of pegcetacoplan, iptacopan, and add-on danicopan versus C5 inhibitors alone, as well as compared to one another. The absence of this evidence may otherwise limit uptake by patients and clinicians to these promising therapies.

Recommendation 4

Support the use of standard quality of life measures for future clinical trials and registries to more reliably demonstrate the value of newer promising therapies for PNH.

Fatigue, hemoglobin, and transfusion avoidance are important patient-centered outcomes. However, they are rarely translated into utility measures that can be incorporated into cost effectiveness analyses. Manufacturers can advance the ability of all stakeholders to understand the broader value of treatment by collecting and reporting commonly used quality of life measures in clinical trials and registries to better value newer promising treatments for PNH compared to existing therapies such as C5 inhibitors which have transformed the illness by controlling the most severe illness manifestations.

Clinicians and Clinical Societies

Recommendation 1

Track the horizon of important emerging therapies and be prepared to issue updated treatment guidelines for patients with PNH in a form that is easy to interpret and use by clinicians, patients, and payers

There are no official treatment guidelines for PNH. Before the availability of newer medications, current recommendations for C5 inhibitors and pegcetacoplan were guided by expert and consensus opinion. Clinical societies should issue an official practice guideline for managing patients with PNH to include newer therapies such as iptacopan and if approved, add-on danicopan. To an

extent often not appreciated by clinicians, payers actively seek out authoritative clinical guidelines and use them as a foundation of prior authorization criteria. Ideally, guidelines should provide information on options to be used by clinicians and patients for shared decision making and offer pragmatic advice about how to select among different therapies for treatment-experienced PNH patients who develop cs-EVH.

Policymakers

Recommendation 1

The value of novel PNH therapies should not be determined exclusively by estimates of long-term cost offsets used in traditional cost-effectiveness analyses alone, particularly when the existing standard of care is acknowledged to be priced significantly higher than reasonable cost-effective levels.

New therapies that improve hemoglobin, fatigue, quality of life, transfusion dependence, and convenience through oral formulations offer the potential for significant value for patients. But that value must be tempered by the extremely high costs of the current standard of care, especially given that treatment is indefinite. When the costs of C5 inhibitors exceed levels that reflect the opportunity cost for new treatments in the health system, simply aggregating those costs over the lifetime of patients and assigning all potential cost offsets to the "value" of the new therapy, magnifies the existing distortion of value and pricing in the US health care system, denying the chance for the health system to recoup some of the cost savings so that innovation can be kept more affordable for all patients. Assigning the full cost offset to novel PNH therapies also creates a distortion in the incentives for innovation, skewing them strongly away from addressing conditions that are either fatal in the short term, such as genetic diseases of newborns, or that have few added health care costs, such as blindness.

Given these contextual factors, all stakeholders and policymakers should avoid using traditional cost-effectiveness analysis alone as a guide to considerations of fair pricing. Capping credit for cost offsets in some way should be explored further as an alternative approach to calculating ranges of fair pricing. This report provided an alternate way to "share savings" from new PNH treatments by offsetting the cost of C5 inhibitors, which substantially reduced the price estimate for iptacopan to achieve commonly acceptable thresholds compared to the traditional approach. This option and other ways to address these broader questions should be considered today to prepare for "fair pricing" of the innovative treatments of tomorrow.

Researchers/Regulators

Recommendation 1

Develop studies to evaluate the long-term durability, safety, and comparative effectiveness of different treatment options for PNH

In conjunction with manufacturers, payers, and patient organizations, researchers should prioritize collecting real-world data in the form of registries for clinical information combined with claims data for medication prescriptions to study the long-term durability of response, safety profiles, and comparative effectiveness of treatments for PNH to better inform practice guidelines. Regarding safety, a better understanding of the long-term risks is needed from nonadherence, which could be estimated using a medication possession ratio from claims data, and from different complement-amplifying conditions such as infections and surgery.

Recommendation 2

Develop prediction models and biomarkers to identify subpopulations of patients who may benefit from specific treatment strategies for PNH

A gap in the current management of patients with PNH shared by clinical experts was an inability to identify which patients are at risk for developing the most feared complications of PNH if treated with a proximal complement inhibitor alone—severe hemolytic anemia and thromboses. While clone size is the best determinant of severity of illness, patients with the same clone size can have substantially different illness course. Thus, new biomarkers and/or the development of more accurate prediction models may better guide treatment selection upfront before complications develop.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Absolute Reticulocyte Count: It refers to the number of reticulocytes in the blood. It usually ranges between 25 × 10^9/L and 150 × 10^9/L.[43]

Breakthrough Hemolysis: Usually defined as the reappearance of at least one symptom of intravascular hemolysis that occurs within blood vessels (e.g. fatigue, high hemoglobin levels in urine, abdominal pain, shortness of breath, anemia, thrombosis, major adverse vascular events, etc.) corresponding with increased levels of lactate dehydrogenase and decreased hemoglobin.[16] The APPLY-PNH trial defined the breakthrough as clinical if either there is a decrease in hemoglobin levels equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days) or if patients present signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms, in presence of laboratory evidence of intravascular hemolysis.[41]

Clinically Significant Extravascular Hemolysis (EVH): EVH is the destruction of red blood cells outside of blood vessels, especially in the spleen or liver. EVH is considered clinically significant when reticulocyte counts increase above 120 x 10^9 per liter and hemoglobin levels decrease to approximately 9.5 grams per deciliter or below and patients require at least one transfusion for treatment.[21] Trial definitions of clinically significant EVH vary slightly.

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale: A measurement of 13 items related to fatigue and its impact on daily life and functioning. Scores range from 0 to 52 with a higher score indicating better fatigue-related quality of life. A change of 5 points is considered a minimal clinically important change in fatigue for patients with PNH.[44]

Hemoglobin Normalization: Defined as hemoglobin levels increasing to above the lower limit of the normal sex-specific range for hemoglobin (12 grams per deciliter for females and 13.5 grams per deciliter for males).[64] Clinical trials used similar values but varied slightly.

Major Adverse Vascular Events (MAVEs): The APPLY-PNH trial defined MAVE as a composite outcome of acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (Budd-Chiari syndrome), mesenteric/visceral arterial, thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolus, renal arterial thrombosis, renal vein thrombosis, thrombophlebitis/deep vein thrombosis, transient ischemic attack, unstable angina or other.[41] Other trials did not provide any definition of MAVE.

PNH Clone Size: Defined as the percentage of cells that are PNH-affected. A cutoff of ≥10% is used in the definition of PNH.[41]

Proximal Complement Inhibitors: These are designed to interfere with the complement cascade presented in the background section at its early stages (i.e., C3 activation). See Figure 1. Hence, these can prevent both intravascular and extravascular hemolysis. The two interventions included in this review, iptacopan and danicopan, along with pegcetacoplan are considered proximal complement inhibitors.

Terminal Complement Inhibitors: These target the terminal part of the complement pathway (i.e., C5 activation) which prevents intravascular hemolysis. As a result of C5 inhibition, upstream C3 activation is increased and can lead to clinically significant EVH in some patients. Both eculizumab and ravulizumab are terminal complement inhibitors.

Transfusion Avoidance: Defined as remaining free from red blood cell transfusions.

Treatment-Naïve: Patients with PNH who have not previously been treated with a C5 inhibitor.

Treatment-Experienced: Patients with PNH who have been treated with a stable regimen of a C5 inhibitor.

A2. Potential Cost-Saving Measures in PNH

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for PNH as these services will be captured in the economic model. Rather, we are seeking services used in the current management of PNH beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with PNH that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

To inform our understanding of patient perspectives, we participated in conversations with eleven stakeholders (the Aplastic Anemia & MDS International Foundation, three individuals with PNH, three clinical experts, three manufacturers, and one payer). Additionally, one patient we spoke with previously shared their experience living with PNH in the ICER patient portal. The feedback received from written input and scoping conversations helped us to understand and discuss the impact of PNH on patients and caregivers described in section two of the evidence report.

C. Clinical Guidelines

There were no available clinical guidelines for PNH at the time of this report. We summarize three consensus statements from three non-US-based clinical expert groups.

Consensus Statement by the Canadian PNH Network[13]

In 2018, hematologists from the Canadian PNH Network (CPNHN) issued a consensus statement on the diagnosis and management of PNH before the availability of ravulizumab or pegcetacoplan. They recommended flow cytometry to confirm the diagnosis of PNH. The CPNHN recommended treatment with eculizumab for confirmed PNH with significant intravascular hemolysis and at least one of the following criteria: symptomatic anemia (regardless of transfusion dependence), thrombosis, renal insufficiency, pulmonary insufficiency, or severe abdominal pain. They also suggested eculizumab be considered for patients with significant intravascular hemolysis and either disabling fatigue or pregnant. For regular breakthrough hemolysis, they recommended either increasing the dose of eculizumab or reducing the time between infusions. They also recommended hematopoietic stem cell transplantation as a last resort for PNH patients with severe bone marrow failure or risk of hematologic malignancy given the considerable toxicity and mortality.

Consensus Statement by the ABHH RBC and Iron Committee [4]

In 2021, experts from the Brazilian Association of Hematology in Sao Paulo, Brazil published a consensus statement on the diagnosis and treatment of PNH with explicit consideration of the impact of cost of therapy on the Brazilian public health system. They recommended supportive care (oral iron supplementation, blood transfusions, short-courses of glucocorticoids for hemolytic episodes) and the use of intravenous eculizumab as first-line therapy for PNH with symptomatic hemolysis plus at least one of the following criteria: severe anemia (hemoglobin < 7g/dL), thrombosis, complications of hemolysis (renal dysfunction or pulmonary hypertension), smooth muscle dysfunction (abdominal pain, dysphagia), or pregnancy.

Consensus Statement by the PNH Education and Study Group[10]

In 2016, experts from the PNH Education and Study Group (PESG) in Turkey issued a consensus statement on PNH diagnosis, follow-up, and treatment. As described above, PESG recommended flow cytometry to confirm diagnosis, supportive care measures, treatment with eculizumab for either symptomatic intravascular hemolysis and/or PNH-related complications (i.e., thrombosis), and hematopoietic stem cell transplantation as a last resort in severe bone marrow failure.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review was patients with PNH. Subpopulations of interest included treatment-naïve and treatment-experienced PNH with clinically significant extravascular hemolysis.

Interventions

The full list of interventions of interest for this review is as follows:

- Iptacopan (Novartis)
- Danicopan (AstraZeneca: Alexion Pharmaceuticals) added to C5 inhibitor therapy

Comparators

Data permitting, compared all the agents to each other and to the following:

- C5 inhibitors:
    - Ravulizumab (Ultomiris®, Alexion Pharmaceuticals)
    - Eculizumab (Soliris®, Alexion Pharmaceuticals)
- Pegcetacoplan (Empaveli®, Apellis Pharmaceuticals)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Hemoglobin improvement
    - Hemoglobin stabilization
    - Hemoglobin level
    - Transfusion avoidance or dependence
    - Thrombotic events
    - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score
    - Health related quality of life
    - Lactate Dehydrogenase (LDH) level
    - Reticulocyte count

    - Major adverse cardiovascular events (MAVEs)
    - Death
    - Adverse events including
        - Breakthrough hemolysis
        - Neisseria infection
        - Treatment-related adverse events
- Other Outcomes
    - Laboratory measures including red blood cell, bilirubin, and haptoglobin levels
    - Adverse events including
        - Abdominal pain
        - Iron deficiency
        - Respiratory tract infection
        - Viral infection

Timing

Evidence on intervention effectiveness was derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient and outpatient settings across the world.

Table D1.1 PRISMA 2020 Checklist[65]

Section and Topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.

	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/ credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for PNH followed established best research methods.[66,67] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[65] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated using the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2 Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews

1	exp paroxysmal nocturnal hemoglobinuria/
2	("Paroxysmal Nocturnal H*emoglobinuria" or "H*emoglobinuria, Paroxysmal Nocturnal" or "Paroxysmal H*emoglobinuria, Nocturnal" or "H*emoglobinuria, Nocturnal Paroxysmal" or "Nocturnal Paroxysmal H*emoglobinuria" or "PNH" or "Paroxysmal H*emoglobinuria" or "Paroxysmal Cold H*emoglobinuria" or "H*emoglobinuria, Paroxysmal Cold" or "Paroxysmal H*emoglobinuria, Cold" or "Cold Paroxysmal H*emoglobinuria" or "H*emoglobinuria, Cold Paroxysmal" or "Marchiafava Micheli Syndrome" or "Syndrome, Marchiafava-Micheli").ti,ab.
3	1 OR 2
4	("iptacopan" OR "lnp 023" OR "lnp 023 aab" OR "lnp023" OR "lnp023 aab" OR "lnp023aab" OR "nvp lnp 023" OR "nvp lnp 023 aab" OR "nvp lnp 023 nx" OR "nvp lnp023" OR "nvp lnp023 aab" OR "nvp lnp023 nx" OR "nvplnp023" OR "nvplnp023aab" OR "nvplnp023nx" OR "iptacopan").ti,ab.
5	("danicopan" OR "ach 0144471" OR "ach 144471" OR "ach 4471" OR "ach0144471" OR "ach144471" OR "ach4471" OR "alxn 2040" OR "alxn2040").ti,ab.
6	("pegcetacoplan" OR "empaveli" OR "apl 2" OR "apl2" OR "aspaveli" OR "APL-2 peptide" OR "APL-2" OR "syfovre").ti,ab.
7	3 AND (4 OR 5 OR 6)
8	7 NOT (animals not (humans and animals)).sh.
9	8 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
10	limit 9 to English language
11	Remove duplicates from 10

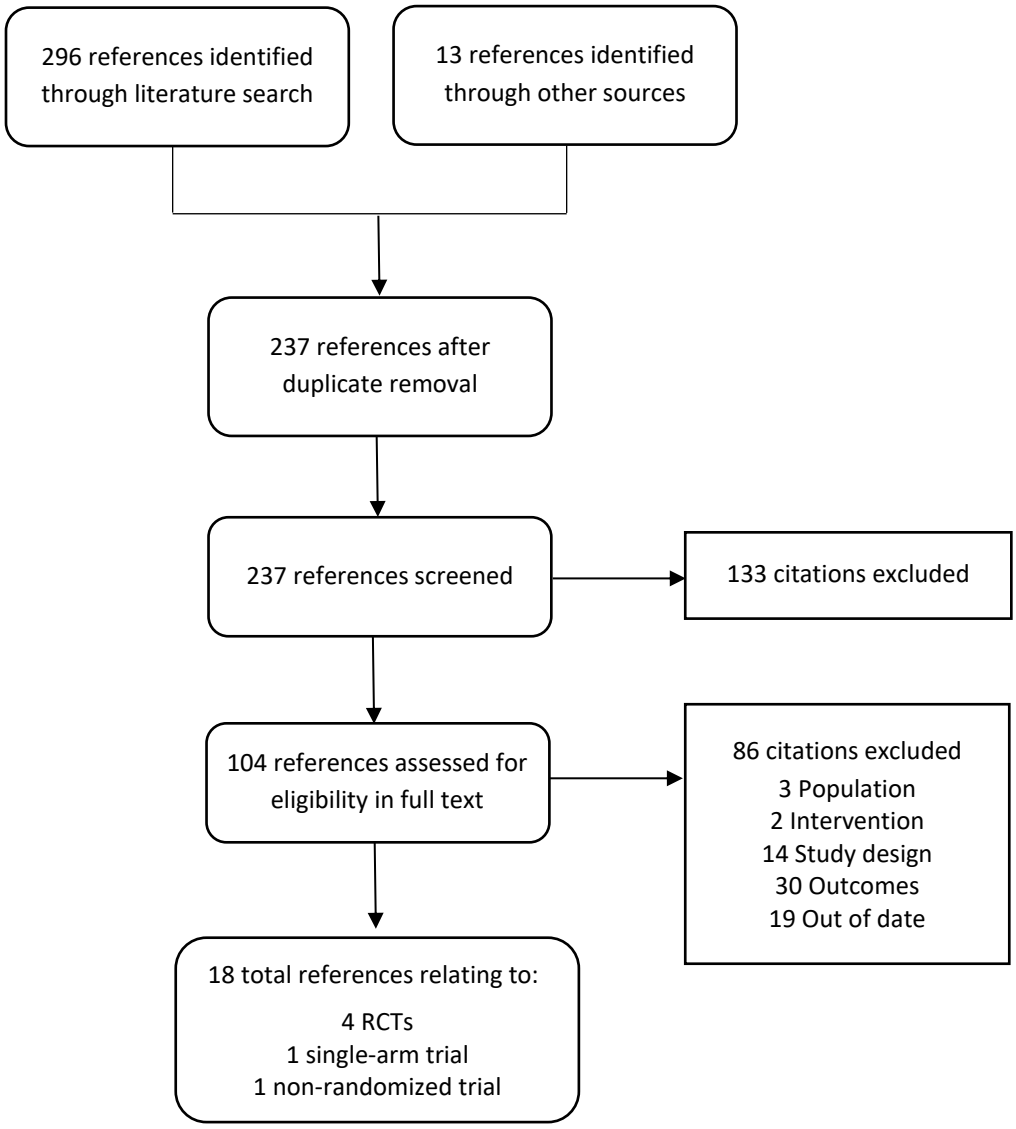
Search last run: January 2, 2024.

Table D1.3 EMBASE Search

1	'paroxysmal nocturnal hemoglobinuria'/exp
2	('haemoglobinuria, nocturnal' OR 'haemoglobinuria, paroxysmal' OR 'haemoglobinuria, paroxysmal nocturnal' OR 'hemoglobinuria, nocturnal' OR 'hemoglobinuria, paroxysmal' OR 'hemoglobinuria, paroxysmal nocturnal' OR 'marchiafava micheli syndrome' OR 'marchiafava syndrome' OR 'nocturnal haemoglobinuria' OR 'nocturnal haemoglobinuria, paroxysmal' OR 'nocturnal hemoglobinuria' OR 'nocturnal hemoglobinuria, paroxysmal' OR 'nocturnal paroxysmal haemoglobinuria' OR 'nocturnal paroxysmal hemoglobinuria' OR 'paroxysmal haemoglobinuria' OR 'paroxysmal hemoglobinuria' OR 'paroxysmal nocturnal haemoglobinuria' OR 'paroxysmal nocturnal hemoglobulinuria' OR 'PNH' OR 'paroxysmal nocturnal hemoglobinuria'):ti,ab
3	#1 OR #2
4	('iptacopan' OR 'lnp 023' OR 'lnp 023 aab' OR 'lnp023' OR 'lnp023 aab' OR 'lnp023aab' OR 'nvp lnp 023' OR 'nvp lnp 023 aab' OR 'nvp lnp 023 nx' OR 'nvp lnp023' OR 'nvp lnp023 aab' OR 'nvp lnp023 nx' OR 'nvplnp023' OR 'nvplnp023aab' OR 'nvplnp023nx' OR 'iptacopan'):ti,ab
5	('danicopan' OR 'ach 0144471' OR 'ach 144471' OR 'ach 4471' OR 'ach0144471' OR 'ach144471' OR 'ach4471' OR 'alxn 2040' OR 'alxn2040'):ti,ab
6	('pegcetacoplan' OR 'empaveli' OR 'apl 2' OR 'apl2' OR 'aspaveli' OR 'APL-2 peptide' OR 'APL-2' OR 'syfovre'):ti,ab
7	#3 AND (#4 OR #5 OR #6)
8	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
9	#7 NOT #8
10	#9 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
11	#10 AND [english]/lim
12	#11 NOT [medline]/lim

Search last run: January 2, 2024.

Figure D1.1 PRISMA flow Chart Showing Results of Literature Search for Iptacopan and Danicopan



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included manufacturer's submission to ICER for iptacopan and danicopan.

Data Extraction

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, and results for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[68,69]

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized narratively in the body of the review and in evidence tables (see Supplement Section D3). Key differences between the studies in terms of the study design, patient characteristics, outcomes, and study quality were discussed in the text of the report. We explored the feasibility of an NMA considering the comparability of clinical trial design, baseline characteristics, and outcome measurements. Based on the heterogeneity across trials, we did not compare trials quantitatively.

Risk of Bias Assessment

We examined the risk of bias for the primary outcomes of APPLY-PNH and ALPHA trials as well as two key secondary endpoints (i.e., transfusion avoidance and FACIT-Fatigue) using Cochrane risk-of-bias tool for randomized trials (RoB 2)[70] and guidance criteria published by Higgins et al (2020).[67] See Table D1.4 below. Risk of bias was assessed for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. To assess the risk of bias in trials in the report, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias". Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias: The study is judged to be at low risk of bias for all domains for this result.
Some concerns: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Although no peer-reviewed full-text publication was available for the APPLY-PNH trial, we still assessed the risk of bias using the available conference abstract, clinicaltrial.gov, and FDA review documents. We did not assess the risk of bias in APPOINT-PNH trial because it was a single-arm study without a comparator. However, we discussed the limitations of this study design in the uncertainty section of the report.

Assessment of Publication Bias

We evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using ClinicalTrials.gov. Search terms included "iptacopan," "danicopan", and "paroxysmal nocturnal hemoglobinuria." We selected studies which would have met our inclusion criteria and for which no findings have been published. We provided a qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Table D1.4. Risk of Bias Assessment

Outcomes Assessed	Randomization Process	Deviation from the Intended Intervention	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Iptacopan: APPLY-PNH Phase 3, Open Label, Randomized Trial						
Primary Endpoint: Increase in Hb levels ≥2 g/dL from baseline or sustained ≥12 g/dL without transfusion	Low	Low	Low	Some concern	Low	**Some concerns**
Proportion of patients achieved transfusion Avoidance	Low	Low	Low	Some concern	Low	**Some concerns**
Change from baseline in FACIT-Fatigue score	Low	Low	Low	High	Low	**High**
Danicopan: ALPHA Phase 3, Double-blind, Randomized Trial						
Primary Endpoint: Change from baseline in Hb level	Low	Low	Low	Low	Low	**Low**
Proportion of patients achieved transfusion Avoidance	Low	Low	Low	Low	Low	**Low**
Change from baseline in FACIT-Fatigue score	Low	Low	Low	Low	Low	**Low**

Hb: hemoglobin, g: grams, dL: deciliter

D2. Additional Clinical Evidence

The main report discusses primary sources of data and key evidence to inform our review of iptacopan and danicopan for the treatment of PNH. In this supplement, we describe additional trial characteristics, baseline data, relevant secondary endpoints from the Phase 3 trials, as well as safety evidence from two Phase 2 trials of these interventions that are not presented in the main report.

Additional Evidence Base

Treatment-Naive to Complement Inhibitors

We discussed the APPOINT-PNH trial for iptacopan in our main report section. This multicenter Phase 3 single-arm trial was conducted outside of the US and concluded its 24-week treatment period on November 2, 2022. The trial design includes a 24-week extension treatment period with only BTH data available to date. Beyond the key inclusion and exclusion criteria mentioned in the main report, vaccinations against Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae were required to be enrolled in the trial. This trial also excluded patients with major concurrent comorbidities as determined by the investigators.[40] Regarding the baseline characteristics, both males and Asians were overrepresented in this trial.[26] Additional trial design, participant characteristics, and key secondary outcomes are provided in Supplement Table D3.1.

Treatment-Experienced with Clinically Significant EVH

We discussed the APPLY-PNH trial for iptacopan and the ALPHA trial for danicopan in the main report. In this section, our primary focus was on the additional Phase 2 trial for each intervention, while also providing supplementary details on trial design, baseline characteristics, and additional results of the preceding two Phase 3 trials.

Iptacopan

The APPLY-PNH is a multinational, open-label trial, with the US being one of the participating countries. The trial design included a 24-week randomized treatment period, a 24-week treatment extension period, and another rollover extension program in which patients randomized to iptacopan will continue iptacopan, but those who are randomized to C5 inhibitors will be switched to iptacopan for 24 more weeks. Data were available for both randomized treatment and extension periods which concluded on September 26, 2022 and March 6, 2023, respectively.[30,41] In addition to the key inclusion and exclusion criteria outlined in the main report, the trial required vaccinations against several infections and excluded participants if they had major severe concurrent comorbidities.[41] The mean duration of treatment with C5 inhibitors was four years for all participants enrolled in this trial and a majority of participants (65%) used eculizumab.[28] Additional

trial design, participant characteristics, and key secondary outcomes are provided in Supplement Table D3.1.

The iptacopan Phase 2 trial had a total of 13 patients randomized to receive either 100 mg or 200 mg of iptacopan for up to 2 years. Adults were included if they had an active diagnosis of PNH with a clone size of ≥10%, a hemoglobin level of < 10.5 g/dL, LDH levels ≥1.5 times the upper limit of normal and did not use complement inhibitor in the three months before treatment intervention. Additional exclusion criteria were a history of known or suspected hereditary complement deficiency, a history of HSCT, laboratory evidence of bone marrow failure, and severe concurrent comorbidities. The primary outcome was the percentage of patients with a reduction of PNH-associated hemolysis at week 12.[32] We included this Phase 2 trial to assess the safety and tolerability of iptacopan.

Danicopan

The Phase 3 ALPHA trial is a multinational placebo-controlled trial enrolling patients from centers across 17 countries, including the US. The trial design included a 12-week randomized treatment period with an additional treatment period of 12 weeks in which participants randomized to placebo will be switched to danicopan plus C5 inhibitor and those who randomized to danicopan will continue along with their C5 therapy. Additional inclusion criteria included thresholds for platelet and neutrophil counts indicative of bone marrow failure.[35] As summarized in the main report, baseline characteristics were comparable between arms. Overall, the enrolled population had a slightly higher representation of female participants and a higher representation of Asian and White participants over other races.[34] Additional trial design, participant characteristics, and key secondary outcomes are provided in Supplement Table D3.1.

In the Phase 2 dose-finding danicopan trial, the investigators enrolled 12 patients to receive danicopan 100 to 200 mg thrice daily as add-on to eculizumab treatment for 24 weeks. Adults were enrolled if they had a diagnosis of PNH, received at least one RBC transfusion within the prior 12 weeks, had anemia with adequate reticulocytosis, and were on a stable regimen of eculizumab. Participants with a history of known or suspected complement deficiency, a history of HSCT, current evidence of bone marrow failure or aplastic anemia, and documented C5 complement protein mutations were excluded. The primary outcome was the change from baseline in hemoglobin at week 24.[39] This Phase 2 trial was included to provide evidence for the safety and tolerability of danicopan.

Additional Clinical Benefits

Treatment-Naïve to Complement Inhibitors

The APPOINT-PNH single-arm trial included PNH patients naïve to complement inhibitors to investigate the efficacy and safety of iptacopan. Excluding five participants who received an RBC transfusion within the first two weeks, the adjusted mean hemoglobin change from baseline at week 24 was 4.3 (95% CI 3.9, 4.7) g/dL.[26] Along with the observed results, the trial also presented efficacy results accounting for missing values. For instance, it was estimated that 92% (95% CI 83, 100) of patients treated with iptacopan had an increase in hemoglobin levels of either ≥2 from baseline and 63% (95% CI 48, 78) sustained hemoglobin levels at or above 12 g/dL without needing transfusions.[26] Additional prespecified analyses using imputed values for missing data supported the results for hematological response outcomes. A prompt decline in mean ARC was observed within the first week of treatment, reaching a mean count of around 69 × 10^9/L by week 24.[26] Baseline mean C3 deposition was minimal and remained consistently low through the end of the follow-up period, suggesting control of EVH.[25] Iptacopan increased PNH clone size by a mean of 43% from baseline at week 24. Greater clone size indicates greater severity of PNH,[11] both in terms of intravascular hemolysis and thrombosis risk, but the clinical significance of the increased clone size in the context of proximal complement inhibitor therapy is unknown. See Supplement Tables D3.3–D3.6.

Treatment-Experienced with Clinically Significant EVH

Iptacopan

Iptacopan was studied in a Phase 3, open-label, randomized APPLY-PNH trial among treatment-experienced PNH patients on a stable regimen of a C5 inhibitor with clinically significant EVH. In addition to the observed data, this trial reported marginal population estimates for several primary and secondary outcomes to account for missing data. Based on the marginal proportions that reflect the study population and adjusted baseline covariates, patients treated with iptacopan had a statistically significantly higher chance of achieving both co-primary endpoints (i.e., sustained hemoglobin of ≥2 or ≥12 g/dL) compared to a C5 inhibitor, with a treatment difference of 80% and 67%, respectively. An estimated 96% of the iptacopan arm would achieve transfusion avoidance in comparison to only 26% of those treated with C5 inhibitors.[28] Iptacopan demonstrated superiority over C5 inhibitors in reducing ARC from baseline, with a treatment difference of -116.2 (95% CI -132, -100; P < 0.0001).[28,33] Iptacopan increased PNH clone size by as early as week 4, increasing 29% from baseline at week 24. Conversely, a reduction in mean C3 deposition was noted by week 4, which further decreased by 19% from baseline at week 24[27]. See Supplement Tables D3.3.–D3.5.

A total of 95 patients, 61 in iptacopan arm and 34 in C5 inhibitor arm, received iptacopan in the additional 24-week extension phase as two patients discontinued treatment in the randomized

period. Available data at week 48 suggests sustained improvements in change from baseline in hemoglobin level, transfusion avoidance, FACIT-fatigue, and other clinically important outcomes.[30] See Supplement Tables D3.7-D3.8.

Danicopan

In the Phase 3, placebo-controlled, double-blinded ALPHA trial, investigators reported the effect of danicopan added on to a C5 inhibitor on secondary endpoints: hemoglobin normalization, absolute reticulocyte count (ARC), PNH clone size, and C3 deposition. At the end of 12 weeks, 29% of the danicopan group had hemoglobin normalization (i.e., above the lower limit of the normal reference range) compared to 0% in the placebo group.[35] A statistically significant decrease in ARC from baseline was also seen in the danicopan versus the placebo add on group, indicating decreased hemolysis in those treated with danicopan (treatment difference: -87.2; $p<0.0001$).[34] Add-on danicopan also decreased the amount of C3 fragment deposition from baseline in 23 assessed patients as compared to 10 add-on placebo participants. Clone size decreased by 3% in the add-on placebo group while it increased by approximately 25% in the add-on danicopan arm.[35] The clinical significance of greater clone size due to proximal complement inhibitor treatment is uncertain but may signify greater risk for hemolysis and thrombosis. See Supplement Tables D3.3.-D3.5.

In the subsequent open-label extension phase, 48 participants (84%) continued their regimen with danicopan, whereas 23 participants (79%) from the placebo arm switched to danicopan with both arms continuing to receive a C5 inhibitor for an additional 12 weeks. Among them, 40 participants (70%) in the danicopan-danicopan arm and 20 participants (69%) in the placebo-danicopan arm completed this second treatment period and entered the long-term extension phase. At week 24, danicopan in addition to C5 inhibitors demonstrated durable response, marked by improvements in hemoglobin levels, similar FACIT-Fatigue score as general public, increased transfusion avoidance, and favorable changes in both LDH and ARC levels.[37]

Additional exploratory analysis of the EORTC-QLQ-C30 suggested that treatment with danicopan led to notable improvements in each subscale (i.e., global health status/QoL, physical functioning, fatigue, nausea and vomiting, appetite loss, constipation, and diarrhea) by week 12. These improvements were maintained, with scores comparable to those of the general population through week 24.[38] See Supplement Tables D3.7-D3.8.

Additional Harms

Iptacopan

The adverse events documented in both Phase 2 and Phase 3 trials of iptacopan were largely comparable. The majority of the adverse events in the Phase 2 trial were mild and moderate in severity, with no instances of serious adverse events reported. There was only one discontinuation

due to a treatment-related adverse event. Four participants experienced a total of nine treatment-related adverse events. The most frequent adverse events in this Phase 2 trial were headache, abdominal discomfort, increased blood alkaline phosphatase, oropharyngeal pain, and upper respiratory tract infection.[32] See Supplement Table D3.6. for more details.

Breakthrough Hemolysis (BTH)

None of the participants in the iptacopan arm experienced breakthrough hemolysis in the APPOINT-PNH trial. In the APPLY-PNH trial, two (3.2%) participants in the iptacopan arm had breakthrough hemolysis as defined in the trial.[29]

In the 24-week open-label extension period, a total of 135 participants from APPOINT-PNH and APPLY-PNH trials received iptacopan with an estimated total exposure of 111 patient years. Two participants (5%) in the APPOINT-PNH trial and six (6%) in the APPLY-PNH trial had clinical BTH during this extension period. Of note, one APPOINT-PNH participant experienced severe BTH for 103 days since the acute BTH event was followed by a chronic hemolytic state and this participant received 8 units of transfusion as intervention. Six (17%) participants in the C5 inhibitor arm had BTH in the treatment period with one classified as severe but limited to a duration of six days. However, the APPLY-PNH trial defined these episodes more broadly than intravascular hemolysis, so these BTH episodes may also include severe EVH. The majority of these BTH cases were confirmed clinically by signs and symptoms except three.[30]

Major Adverse Vascular Events (MAVE)

In the Phase 3 APPLY-PNH trial, one participant from each of the iptacopan and C5 inhibitor arms experienced a MAVE during week 24 to week 48 of treatment.[30]

Danicopan

In the Phase 2 trial, danicopan was generally well tolerated over the 24-week treatment period. All 12 enrolled participants receiving danicopan experienced at least one adverse event, mostly mild to moderate in severity. The most common adverse events were headache, cough, and nasopharyngitis. Four participants experienced a severe adverse event. None were deemed related to danicopan and resolved, but one resulted in a treatment discontinuation from the trial after two doses of the study drug.[39] Safety results from the Phase 3 ALPHA trial summarized in the main report are consistent with these Phase 2 results. See Supplement Tables D3.6 for more detail.

D3. Evidence Tables

Table D3.1. Study Design

Trial	Study Design	Treatment Arms	Included Population	Key Outcomes [Timepoint]
Iptacopan				
APPOINT-PNH[40]	**Phase 3** Multicenter, open-label, single-arm trial N = 40 NCT04820530	Arm I **Iptacopan:** 200 mg taken orally twice a week	- Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with clone size ≥ 10% - Mean hemoglobin level <10 g/dL - LDH > 1.5 x Upper Limit of Normal (ULN)	- Improvement of hemoglobin levels from baseline ≥2 g/dL or levels sustained ≥12 g/dL with no RBC transfusions (Week 24) - Reticulocyte counts, LDH, FACIT-fatigue, breakthrough hemolysis and MAVE rates (Week 24) - Transfusion avoidance (Week 24) - Change from baseline in Hb (Week 24)
APPLY-PNH[41]	**Phase 3** Randomized multi-center, open-label active-comparator controlled trial N = 97 NCT04558918	Arm I **Iptacopan:** 200 mg orally twice a week Arm II **Ravulizumab**: 30mg/30mL IV infusion every 8 weeks **or Eculizumab:** 30mg/30mL IV infusion every 2 weeks	- Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with clone size ≥ 10% - Stable regimen of anti-C5 antibody treatment (eculizumab or ravulizumab) for at least 6 months prior to randomization - Mean hemoglobin level <10 g/dL - Excluded HSCT	- Improvement of hemoglobin levels from baseline ≥2 g/dL or levels sustained ≥12 g/dL with no RBC transfusions (Week 24) - Reticulocyte counts, LDH, FACIT, breakthrough hemolysis and MAVE rates (Week 24) - Change from baseline in hemoglobin - Participants who remain free from transfusions (Week 24)
Danicopan				
ALPHA[35]	**Phase 3** Randomized multi-center, double blinded, placebo controlled trial N = 86 NCT04469465	Arm I: **Danicopan + C5 inhibitor** Arm II: **Placebo + C5 inhibitor**	- Diagnosis of PNH clinically evident EVH defined by anemia (Hb ≤9.5 g/dL) with absolute reticulocyte count ≥120 x 10^9/L - Receiving a C5 inhibitor for at least 6 months prior to Day 1 - Platelet count ≥30,000/microliters (µL) - Absolute neutrophil counts ≥500/µL - Excluded HSCT and known aplastic anemia/bone marrow failure requiring HSCT or other therapies	- Change From Baseline in Hemoglobin (Week 12) - Change From Baseline in FACIT-Fatigue Scores (Week 12) - Transfusion Avoidance (Week 12) - Change From Baseline in Absolute Reticulocyte Count (Week 12)

Trial	Study Design	Treatment Arms	Included Population	Key Outcomes [Timepoint]
Pegcetacoplan				
PEGASUS[71]	**Phase 3** Randomized multi-center, open-label, active-comparator controlled trial N = 80 NCT03500549	Arm I: **Pegcetacoplan:** 1080 mg subcutaneous, twice-weekly or every three days. Arm II: **Eculizumab**	- Primary diagnosis of PNH - On treatment with eculizumab stable for ≥3 months prior to screening - Hb <10.5 g/dL at screening - Absolute reticulocyte count > 1.0x ULN - Platelet count of >50,000/mm3 - Absolute neutrophil count >500/mm3 - Excluded HSCT and hereditary complement deficiency	- Mean Change From Baseline in Hemoglobin (Hb) Level (Week 16) - Transfusion avoidance (Week 16) - Reticulocyte counts, LDH, FACIT, Hb response in the absence of transfusion (Week 16)

dL: deciliter, FACIT: functional assessment of chronic illness therapy, g: grams, Hb: hemoglobin, HSCT: hemopoietic stem cell transplant, IV: intravenous, L: liter, LDH: lactate dehydrogenase, MAVE: major adverse cardiovascular event, mg: milligram, mm: millimeter, N: total number, PNH: paroxysmal nocturnal hemoglobinuria, ULN: upper limit of normal

Table D3.2. Baseline Characteristics

Drug		Iptacopan			Danicopan		Pegcetacoplan	
Trial		APPOINT-PNH[26,33]	APPLY-PNH[28,33]		ALPHA[34,35,37]		PEGASUS[2]	
Treatment Arm		Iptacopan	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i	Danicopan	Eculizumab
N		40	62	35	57	29	41	39
Age, years	Mean (SD)	42.1 (15.9)	51.7 (16.9)	49.8 (16.7)	52.8 (17.0)	52.9 (14.3)	50.2 (NR)	47.3 (NR)
	Median (range)	38.5 (18-81)	53 (22-84)	45 (20-82)	NR (20, 82)	NR (29, 77)	NR (19-81)	NR (23-78)
Time since diagnosis, years (SD)		4.7 (5.5)	11.9 (9.8)	13.6 (10.9)	NR	NR	6.0 (NR)	9.7 (NR)
Sex, n (%)	Female	17 (42.5)	43 (69.4)	24 (68.6)	34 (59.6)	20 (69.0)	27 (66)	22 (56)
	Male	23 (57.5)	19 (30.6)	11 (31.4)	23 (40.4)	9 (31.0)	14 (34)	17 (44)
Race, n (%)	Asian	27 (67.5)	12 (19.4)	7 (20.0)	22 (38.6)	10 (34.5)	5 (12)	7 (18)
	Black	1 (2.5)	2 (3.2)	2 (5.7)	2 (3.5)	0	2 (5)	0
	White	12 (30)	48 (77.4)	26 (74.3)	28 (49.1)	14 (48.3)	24 (59)	25 (64)
	Indigenous	0	0	0	1 (1.8)	0	NR	NR
	Other	0	0	0	1 (1.8)	0	0	1 (3)
	Not Reported	0	0	0	3 (5.3)	4 (13.8)	10 (24)	6 (15)
Disease Duration, years	Mean (SD)	4.7 (5.5)	11.9 (9.8)	13.5 (10.9)	NR	NR	NR	NR
	Median (range)	3.6 (0.01-23.2)	9.0 (0.7-40.2)	11.6 (1.5-42)	NR	NR	NR	NR

Drug		Iptacopan			Danicopan		Pegcetacoplan	
Trial		APPOINT-PNH[26,33]	APPLY-PNH[28,33]		ALPHA[34,35,37]		PEGASUS[2]	
Treatment Arm		Iptacopan	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i	Danicopan	Eculizumab
Hemoglobin g/dL	**Mean (SD)**	8.2 (1.1)	8.9 (0.7)	8.9 (0.9)	7.67 (0.95)	7.89 (1.01)	8.69 (1.08)	8.68 (0.89)
	Median (range)	NR (5.8, 10.0)	NR (6.8, 10.0)	NR (6.2, 9.9)	NR	NR	NR	NR
LDH* IU/L	**Mean (SD)**	1698.8 (683)	269.1 (70.1)	272.7 (84.8)	304 (123.6)	286.4 (93.1)	257.5 (97.6)	308.6 (284.8)
	Median (range)	1582 (522, 244)	268 (150, 539)	261 (133, 562)	NR	NR	NR	NR
ARC† $x10^9$/L	**Mean (SD)**	154.3 (63.7)	193.2 (83.6)	190.6 (80.9)	248 (97)	223 (115)	217.5 (75.0)	216.2 (69.1)
	Median (range)	139 (59, 325)	177 (51, 563)	160 (90, 412)	NR	NR	NR	NR
FACIT-Fatigue Score	**Mean (SD)**	32.8 (10.2)	34.7 (9.8)	30.8 (11.5)	34.2 (11.0)§	33.6 (10.7)§	32.2 (11.4)	31.6 (12.5)
	Median (range)	34.3 (13-51)	34.8 (11-52)	31.5 (10-50)	NR	NR	NR	NR
No. of RBC Transfusions in prior year‡	**Mean (SD)**	3.1 (2.09)	3.1 (2.58)	4.0 (4.34)	2.6 (2.1)§	2.3 (1.4)§	NR	NR
	Median (range)	2 (1-8)	2 (1-13)	2 (1-19)	2 (0, 10)	2 (0, 8)	NR	NR
	N with 0	12 (30)	27 (43.5)	14 (40)	NR	NR	10 (24)	10 (26)
	N with >0	28 (70)	35 (56.5)	21 (60.0)	49/49 (100) §	24/24 (100) §	31 (76)	29 (74)
C5 Inhibitors, n (%)	**Eculizumab**	N/A	40 (64.5)	23 (65.7)	21 (36.8)	14 (48.3)	41 (100)	39 (100)
	Ravulizumab	N/A	22 (35.5)	12 (34.3)	36 (63.2)	15 (51.7)	0	0
	Mean duration, years (SD)	N/A	3.8 (3.6)	4.2 (3.9)	NR	NR	4.4 (0.4-17.1)	3.4 (0.3-13.8)
History of MAVEs, n (%)	**No**	35 (87.5)	50 (80.6)	25 (71.4)	NR	NR	NR	NR
	Yes	5 (12.5)	12 (19.4)	10 (28.6)	NR	NR	NR	NR

ARC: absolute reticulocyte count, dL: deciliter, FACIT: The Functional Assessment of Chronic Illness Therapy, g: grams, IU: international units, L: liter, LDH: lactate dehydrogenase, n: number, N: total number, No: number, RBC: red blood cell, SD: standard deviation

* Normal range for LDH is around 140 to 280 U/L.[42]

† Normal range for ARC is around 25×10^9/L and 150×10^9/L.[43]

‡ In the 6 months prior to randomization for APPLY-PNH and APPOINT-PNH

§ Data only provided for 49 danicopan treated patients and 24 placebo arm patients.

Table D3.3. Hemoglobin-Related Efficacy Outcomes

Drug	Iptacopan			Danicopan		Pegcetacoplan	
Trial	**APPOINT-PNH**[26]	**APPLY-PNH**[28,33]		**ALPHA**[34,35]		**PEGASUS**[2]	
Treatment Arm	**Iptacopan**	**Iptacopan**	**C5i**	**Danicopan + C5i**	**Placebo + C5i**	**Pegcetacoplan**	**Eculizumab**
Timepoint	24 weeks	24 weeks		12 weeks		16 weeks	
N	40	62	35	42	21	41	39
Hemoglobin Level (g/dL)							
Mean Hemoglobin (SD)	12.56 (1.49)	*12.6 (1.5)*	*9.1 (1.4)*	10.75 (1.4)	8.46 (1.13)		
Change From Baseline, Mean (95% CI)	4.28 (3.87, 4.70)	3.6 (NR)	-0.1 (NR)	NR	NR	NR	NR
Change From Baseline, Least Squares Mean (SE)	NR	NR	NR	2.94 (0.21)	0.50 (0.31)	2.37 (0.36)	-1.47 (0.67)
Treatment Difference (95%CI); p-value	N/A	3.7 (3.2, 4.1); p<0.0001		2.44 (1.69, 3.20); p<0.0001		3.84 (2.33, 5.34); p<0.001	
Participants with an Increase in Hemoglobin ≥2g/dL from Baseline in the Absence of Blood Transfusions							
n/N (%) [% estimate*]	31/33‡ (93.9) [92.2]	51/60† (85) [82.3]	0/35 (0) [2.0]	25 (59.5)	0	NR	NR
Treatment Difference (95%CI); p-value	N/A	80.3 (71.3, 87.60); p<0.0001		46.9 (29.2, 64.7); p<0.0001		NR	
Participants with Hemoglobin Levels ≥12g/dL in the Absence of Blood Transfusions (Hemoglobin Normalization§)							
n/N (%) [% estimate*]	19/33‡ (57.6) [62.8]	42/60† (70) [68.8]	0/35 (0) [1.8]	12/42 (28.6)	0	14/41 (34.1)	0
Treatment Difference (95%CI); p-value	N/A	67.0 (56.3, 76.9); p<0.0001		18.4 (-0.84, 37.7); p=0.0080		Risk Difference: 30.4 (14.9, 45.9)	

Italicized data have been digitized from figures; interpret with caution.

* Estimate based on missing hemoglobin values imputed for one patient

† 2 patients had missing data from week 18 to 24 and were not evaluable

‡ 7 patients had missing data between week 18 to 24 and were not evaluable

95%CI: 95 percent confidence interval, dL: deciliter, FACIT: The Functional Assessment of Chronic Illness Therapy – Fatigue, g: grams, LDH: lactate dehydrogenase, LSM: least squares mean, n: number, N: total number, SD: standard deviation, , SE: standard error

§ Hemoglobin normalization thresholds in ALPHA & PEGASUS trials: ALPHA (males >12.5 g/dL , females >11.0 g/dL), PEGASUS (females ≥12–16 g/dL, males ≥13.6–18 g/dL)

Table D3.4. Other Efficacy Outcomes

Drug	Iptacopan			Danicopan		Pegcetacoplan	
Trial	**APPOINT-PNH**[24-26]	**APPLY-PNH**[27,28,33]		**ALPHA**[34,35,37]		**PEGASUS**[2]	
Treatment Arm	**Iptacopan**	**Iptacopan**	**C5i**	**Danicopan + C5i**	**Placebo + C5i**	**Pegcetacoplan**	**Eculizumab**
Timepoint	24 weeks	24 weeks		12 weeks		16 weeks	
N	40	62	35	42	21	41	39
Participants Achieving Transfusion Avoidance							
n/N (%) [% estimate]*	40/40 (100) [97.6]	59/62 (95.2) [96.4]	14/35 (40) [26.1]	35 (83.3)	8 (38.1)	35/41 (85)	6/39 (15)
Treatment Difference (95%CI); p-value	N/A	68.9 (51.4, 83.9)s; p<0.0001		41.7 (22.7, 60.8); p=0.0004		63 (48, 77); p<0.001	
Participants with Breakthrough Hemolysis							
n/N (%)	0	2/62 (3.2)	6/35 (17.1)	2/49 (4)	0/24 (0)	4 (10)	9 (23)
Adjusted Annual Rate (95%CI)	0 (0.0, 0.17)	0.07 (0.02, 0.31)	0.67 (0.26, 1.72)	NR	NR	NR	NR
Rate Ratio; p-value	N/A	0.10 (0.02, 0.61); p=0.0118		NR	NR	NR	NR
Lactated Dehydrogenase (LDH) Level, U/L							
Mean LDH (SD)	261 (89)	*277 (117)*	*283 (127)*	268.2 (61.4)	328.4 (224.3)	189.1	353.2
Change from Baseline, Mean (95% CI)	-83.6[†] (-84.9, -82.1)	0.96[‡] (0.90, 1.03)	0.98[‡] (0.89, 1.07)	NR	NR	NR	NR
Change from Baseline, Least Squares Mean (SE)	NR	NR	NR	-23.5 (8.3)	-2.92 (11.9)	-15 (42.7)	-10 (71.0)
Treatment Difference (95%CI); p-value	N/A	-1.15% (-10.18, 11.32); 0.8345		-20.6 (NR)		-5.0 (-181.3, 172.0)	
Absolute Reticulocyte Count (ARC), 10^9 cells/L							
Mean ARC (SD)	69.05 (22.14)	*72.1 (42.8)*	*177.9 (81.7)*	155.5 (NR)	246.4 (NR)	77.1	220.8
Change from Baseline, Mean (95% CI)	-82.48 (-89.33, -75.62)	-115.8 (NR)	0.3 (NR)	NR	NR	NR	NR
Change from Baseline, Least Squares Mean (SE)	NR	NR	NR	-83.8 (8.9)	3.5 (12.7)	-136 (6.5)	28 (11.9)
Treatment Difference (95%CI); p-value	N/A	-116.2 (-132.0, -100.3); p<0.0001		-87.2 (-117.7, -56.7); p<0.0001		-164.0 (-189.9, -137.3)	
FACIT-Fatigue Score							
Mean Score (SD)	43.9 (6.24)	*43.3 (8.0)*	*30.9 (13.0)*	42.1 (NR)	35.5 (NR)	41.8	30.8
Change from Baseline, Mean (95% CI)	10.75 (8.7, 12.8)	8.59 (6.7, 10.5)	0.31 (-2.2, 2.8)	NR	NR	NR	NR

Drug	Iptacopan			Danicopan		Pegcetacoplan	
Trial	APPOINT-PNH[24-26]	APPLY-PNH[27,28,33]		ALPHA[34,35,37]		PEGASUS[2]	
Treatment Arm	Iptacopan	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i	Pegcetacoplan	Eculizumab
Change from baseline, Least Squares Mean (SE)	NR	NR	NR	7.97 (1.13)	1.85 (1.58)	9.2 (1.6)	-2.7 (2.8)
Treatment difference (95%CI); p-value	N/A	8.29 (5.28, 11.29); p<0.0001		6.12 (2.33, 9.91); p=0.0021		11.9 (5.5, 18.3); NR	
PNH Clone Size, Mean % (SD)							
at Baseline	43.9	64.6	*57*	NR	NR	66.8 (26.5)	72.9 (25.8)
at Last Follow-up	87.1	93.2	*60*	NR	NR	93.9 (6.4)	62.6 (26.0)
Change from Baseline	43.2 (18.9)	28.6 (NR)	NR	24.60 (4.18)	-3.04 (5.86)	27.7 (24.5)	-9.7 (14.6)
C3 Deposition, Mean (SD)							
at Baseline	0.67	19.2	*18*	29.4 (20.3)	31.6 (20.3)	17.7 (13.5)	19.8 (15.0)
at Last Follow-up	0.11	0.3	*14*	12.7 (16.7)	36.5 (19.1)	0.2 (0.3)	16.9 (15.5)
Change from Baseline	0.56 (NR)	-19.2 (NR)	NR	-15.06 (2.82)	0.89 (4.39)	-17.9 (12.8)	-3.2 (10.5)

Italicized data have been digitized from figures; interpret with caution.

95%CI: 95 percent confidence interval, dL: deciliter, g: grams, LDH: lactate dehydrogenase, LSM: least squares mean, n: number, N: total number, SD: standard deviation, SE: standard error

* Estimate based on missing hemoglobin values imputed for one patient

† Adjusted mean percentage change from baseline

‡ Adjusted geometric mean ratio to baseline in log-transformed LDH

Table D3.5. Exploratory Health-Related Quality of Life (HRQoL) Measures

Drug	Iptacopan			Danicopan	
Trial	APPOINT-PNH[25,26,30]	APPLY-PNH[27,28,30]		ALPHA[34-36]	
Treatment Arm	Iptacopan	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i
Timepoint	24 weeks	24 weeks		12 weeks	
N	40	62	35	42	21
EQ-5D-3L Score					
Change from baseline, LSM (95%CI)	NR	NR	NR	0.06 (0.03, 0.09)	0.06 (0.01, 0.1)
Treatment difference (95%CI); p-value	NR	NR		0 (-0.05, 0.05); p=0.8903	
EORTC QLQ-C30 Score: Physical Functioning*					
Change from baseline, LSM (95%CI)	NR	NR	NR	8.10 (3.6, 12.6)	-2.84 (-9.4, 3.7)
Treatment difference (95%CI); p-value	NR	NR		10.94 (3.15, 18.73); p=0.0067	

Drug	Iptacopan			Danicopan	
Trial	**APPOINT-PNH**[25,26,30]	**APPLY-PNH**[27,28,30]		**ALPHA**[34-36]	
Treatment Arm	**Iptacopan**	**Iptacopan**	**C5i**	**Danicopan + C5i**	**Placebo + C5i**
Responder analysis threshold: 18-points, % (95% CI)	41 (29, 53)	40 (32, 48)	9 (5, 13)	NR	NR
EORTC QLQ-C30 Score: Social Functioning*					
Change from baseline, LSM (95%CI)	NR	NR	NR	7.52 (0.83, 14.2)	-6.61 (-16.3, 3.1)
Treatment difference (95%CI); p-value	NR	NR		14.13 (2.62, 25.7); p=0.0171	
EORTC QLQ-C30 Score: Role Functioning					
Responder analysis threshold: 18-points, % (95% CI)	NR	39 (31, 47)	15 (10, 20)	NR	NR
Responder analysis threshold: 22-points, % (95% CI)	46 (34, 58)	NR	NR	NR	NR
EORTC QLQ-C30 Score: Fatigue Symptoms*					
Change from baseline, LSM (95%CI)	NR	NR	NR	13·54 (-20·6, -6·5)	1·06 (-9·1, 11·3)
Treatment difference (95%CI); p-value	NR	NR		-14·60(-26·7, 2·5); p=0.0192	
Responder analysis threshold: 20-points, % (95% CI)	NR	49 (41, 56)	14 (9, 19)	NR	NR
Responder analysis threshold: 25-points, % (95% CI)	46 (34, 59)	NR	NR	NR	NR
EORTC QLQ-C30 Score: Dyspnea Symptoms					
Responder analysis threshold: 21-points, % (95% CI)	NR	46 (38, 54)	20 (14, 27)	NR	NR
Responder analysis threshold: 16-points, % (95% CI)	55 (42, 68)	NR	NR	NR	NR
WPAI:ANSc Actual Values at Week 12, [n assessed] Mean (SD)					
Employed, n (%)	NR	NR	NR	24 (57)	6 (29)
Hours missed work due to anemic symptoms	NR	NR	NR	[25] 7.4 (16.04)	[8] 0
Hours missed work due to other reasons	NR	NR	NR	[25] 5.0 (7.92)	[8] 4.8 (8.41)
Hours worked	NR	NR	NR	[25] 29.5 (20.9)	[8] 20.3 (14.11)
How much anemic symptoms affect work productivity	NR	NR	NR	[24] 2.3 (2.83)	[8] 3.3 (3.58)
How much anemic symptoms affect ability on non-work regular daily activities	NR	NR	NR	[39] 2.7 (2.57)	[20] 4.4 (2.80)
HRU Actual Values at Week 12, [n assessed] Mean (SD)					
How many times visited the health care provider for treatment of PNH?	NR	NR	NR	[39] 1.0 (1.09)	[19] 0.7 (0.99)
How many times gone to an emergency room for treatment of PNH?	NR	NR	NR	[39] 0	[19] 0
How many times admitted to a hospital for treatment of PNH?	NR	NR	NR	[39] 0.1 (0.48)	[19] 0.3 (0.65)
How many times had darkened urine?	NR	NR	NR	[39] 2.1 (7.00)	[19] 0.3 (0.73)

Drug	Iptacopan			Danicopan	
Trial	APPOINT-PNH[25,26,30]	APPLY-PNH[27,28,30]		ALPHA[34-36]	
Treatment Arm	Iptacopan	Iptacopan	C5i	Danicopan + C5i	Placebo + C5i
How many times miss work as a result of symptoms of PNH?	NR	NR	NR	[38] 2.4 (8.20)	[19] 2.1 (5.98)

95%CI: 95 percent confidence interval, dL: deciliter, EQ-5D-3L: EuroQoL 5 dimensions Three-level version, EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale, FACIT: The Functional Assessment of Chronic Illness Therapy – Fatigue, HRU: Healthcare Resource Utilization Patient Questionnaire, LSM: least squares mean, n: number, N: total number, SD: standard deviation, WPAI:ANS: Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms version 2.0, QoL: quality of life

* For the ALPHA trial, other domains of the EORTC Functioning and Symptom Scales measured are not listed here due to lack of statistically significant differences between arms such as role, emotional, cognitive function and symptoms like nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

Table D3.6. Adverse Events

Drug	Iptacopan				Danicopan			Pegcetacoplan	
Trial	Phase 2[32]	APPOINT-PNH[26]	APPLY-PNH[28,33]		Phase 2[39]	ALPHA[34,35,37]		PEGASUS[2]	
Treatment Arm	Iptacopan	Iptacopan	Iptacopan	C5i	Danicopan	Danicopan + C5i	Placebo + C5i	Pegcetacoplan	Eculizumab
Timepoint	12 weeks	24 weeks	24 weeks		24 weeks	12 weeks		16 weeks	
N	6	40	62	35	12	57	29	41	39
Adverse Events, n (%)									
Overall	5 (83.3)	37 (93)	51 (82.3)	28 (80.0)	12 (100)	35/49* (71)	14/22* (63)	36 (88)	34 (87)
Serious	0	4 (10)	6 (9.7)	5 (14.3)	NR	3 (5.3)	2 (6.9)	7 (17)	6 (15)
Non-Serious	NR	NR	34 (54.8)	21 (60)	NR	42 (73.7)	18 (62.1)	NR	NR
Mild	4 (66.7)	26 (65)	20 (32.3)	13 (37.1)	NR	NR	NR	NR	NR
Moderate	1 (16.7)	10 (25)	28 (45.2)	12 (34.3)	NR	NR	NR	NR	NR
Severe	0	1 (3)	3 (4.8)	3 (8.6)	4 (33.3)	NR	NR	NR	NR
Treatment-related Adverse Events, n (%)									
Overall	3 (50)	NR	NR	NR	0	NR	NR	NR	NR
Serious	NR	NR	NR	NR	0	NR	NR	NR	NR
Discontinuation, n (%)									
Overall	NR	0	1[†]	0	0	2 (3.5)	1 (3.4)	3 (7.3)	0
AE-related	1 (16.7)	0	0	0	1	2 (3.5)	1 (3.4)	3 (7.3)	0

Drug	Iptacopan				Danicopan			Pegcetacoplan	
Trial	**Phase 2**[32]	**APPOINT-PNH**[26]	**APPLY-PNH**[28,33]		**Phase 2**[39]	**ALPHA**[34,35,37]		**PEGASUS**[2]	
Treatment Arm	**Iptacopan**	**Iptacopan**	**Iptacopan**	**C5i**	**Danicopan**	**Danicopan + C5i**	**Placebo + C5i**	**Pegcetacoplan**	**Eculizumab**
Treatment-related	1 (16.7)	0	0	0	0	NR	NR	NR	NR
BTH-related	NR	0	0	0	0	0*	0*	NR	NR
Mortality, n (%)									
Overall	0	0	1[§]	0	0	0	0	0	0
AE-related	0	0	0	0	0	0	0	0	0
Treatment-related	0	0	0	0	0	0	0	0	0
Adverse Events of Special Interest, n (%)									
Breakthrough hemolysis	NR	0	2 (3.2)	6 (17.1)	NR	2 (4)	0	4 (10)	9 (23)
Abdominal pain	NR	NR	4 (6.5)	1 (2.9)	2 (16.7)	NR	NR	5 (12)	4 (10)
Anemia	NR	NR	NR	NR	NR	1 (1.75)	3 (10.34)	0	5(13)
Arthralgia	NR	NR	5 (8.1)	1 (2.9)	2 (16.7)	4 (7.02)	2 (6.90)	NR	NR
Asthenia	NR	NR	NR	NR	NR	0	4 (13.79)	3 (7)	3 (8)
Back pain	NR	NR	NR	NR	NR	NR	NR	3 (7)	4 (10)
Cough	NR	NR	NR	NR	3 (25)	NR	NR	NR	NR
Contusion	NR	NR	NR	NR	NR	1 (1.75)	3 (10.34)	NR	NR
COVID-19	NR	6 (15)	5 (8.1)	9 (25.7)	NR	NR	NR	NR	NR
Diarrhea	NR	3 (7.5)	9 (14.5)	2 (5.7)	NR	4 (7.02)	3 (10.34)	9 (22)	1 (3)
Dizziness	NR	NR	4 (6.5)	0	NR	1 (1.75)	2 (6.90)	1 (2)	4 (10)
Fatigue	NR	NR	NR	NR	2 (16.7)	NR	NR	2 (5)	6 (15)
Headache	3 (50)	11 (27.5)	10 (16.1)	1 (2.9)	3 (25)	6 (10.53)	2 (6.90)	3 (7)	9 (23)
Hypertension	NR	NR	NR	NR	NR	3 (5.26)	1 (3.45)	3 (7)	1 (3)
Increased blood LDH	NR	NR	4 (6.5)	3 (8.6)	NR	NR	NR	NR	NR
Injection-site reaction	NR	NR	NR	NR	NR	NR	NR	5 (12)	0
Infections	NR	NR	NR	NR	NR	NR	NR	12 (29)	10 (26)
Upper respiratory tract infection	NR	5 (12.5)	2 (3.2)	3 (8.6)	NR	NR	NR	2 (5)	2 (5)
Urinary tract infection	NR	NR	5 (8.1)	1 (2.9)	NR	2 (3.51)	1 (3.45)	NR	NR
Liver enzyme elevations	NR	NR	NR	NR	NR	6 (12.2)	2 (8.3)	NR	NR
MAVEs	NR	0	1 (1.6)[‡]	0	NR	NR	NR	NR	NR
Nasopharyngitis	NR	NR	7 (11.3)	2 (5.7)	3 (25)	NR	NR	NR	NR
Nausea	NR	NR	6 (9.7)	1 (2.9)	2 (16.7)	5 (8.77)	3 (10.34)	2 (5)	2 (5)

Drug	Iptacopan				Danicopan			Pegcetacoplan	
Trial	Phase 2[32]	APPOINT-PNH[26]	APPLY-PNH[28,33]		Phase 2[39]	ALPHA[34,35,37]		PEGASUS[2]	
Treatment Arm	Iptacopan	Iptacopan	Iptacopan	C5i	Danicopan	Danicopan + C5i	Placebo + C5i	Pegcetacoplan	Eculizumab
Pyrexia	NR	NR	NR	NR	NR	3 (5.26)	0	2 (5)	2 (5)
Thrombotic event	0	0	1 (1.6)	0	NR	NR	NR	0	0
Vomiting	NR	NR	NR	NR	NR	3 (5.26)	0	0	3 (8)
Serious Adverse Events, n (%)									
Anemia	NR	NR	NR	NR	NR	0	1 (3.45)	0	2 (5.13)
Abdominal Pain	NR	NR	NR	NR	NR	0	1 (3.45)	0	1 (2.56)
Acute kidney injury	NR	NR	0	1 (2.86)	NR	NR	NR	NR	NR
Arthritis bacterial	NR	NR	0	1 (2.86)	NR	NR	NR	NR	NR
Bacterial infection	NR	NR	NR	NR	NR	NR	NR	1 (2.44)	0
Bacterial pneumonia	NR	1 (3)	NR	NR	NR	NR	NR	NR	NR
Basal cell carcinoma	NR	NR	1 (1.61)	0	NR	NR	NR	NR	NR
Bilirubinuria	NR	NR	0	1 (2.86)	NR	NR	NR	NR	NR
Blood bilirubin increased	NR	NR	NR	NR	NR	1 (1.75)	0	0	1 (2.56)
Breakthrough hemolysis	NR	0	0	1 (2.86)	NR	NR	NR	NR	NR
Cataract	NR	1 (3)	NR	NR	NR	NR	NR	NR	NR
Cholecystitis	NR	NR	NR	NR	NR	1 (1.75)	0	NR	NR
COVID-19	NR	1 (3)	1 (1.61)	2 (5.71)	NR	1 (1.75)	NR	NR	NR
Dyspnoea	NR	NR	NR	NR	NR	NR	NR	1 (2.44)	0
Extravascular haemolysis	NR	0	0	1 (2.86)	NR	NR	NR	NR	NR
Facial paralysis	NR	NR	NR	NR	NR	NR	NR	1 (2.44)	0
Gastroenteritis	NR	NR	NR	NR	NR	NR	NR	1 (2.44)	0
Headache	NR	NR	NR	NR	NR	0	1 (3.45)	NR	NR
Hemolysis	NR	0	0	2 (3.2)	NR	NR	NR	2 (5)	1 (3)
Influenza A virus	NR	NR	0	1 (2.86)	NR	NR	NR	NR	NR
Intervertebral discitis	NR	NR	0	1 (2.86)	NR	NR	NR	NR	NR
Infection/infestation	NR	2 (5.0)	2 (3.2)	3 (8.6)	NR	NR	NR	NR	NR
Jaundice	NR	NR	0	1 (2.86)	NR	NR	NR	0	1 (2.56)
Myelodysplastic syndrome	NR	NR	1 (1.61)	0	NR	NR	NR	NR	NR
Pancreatitis	NR	NR	NR	NR	NR	1 (1.75)	0	NR	NR
Pneumonia	NR	NR	NR	NR	1 (8.3)	NR	NR	NR	NR

Drug	Iptacopan				Danicopan			Pegcetacoplan	
Trial	**Phase 2**[32]	**APPOINT-PNH**[26]	**APPLY-PNH**[28,33]		**Phase 2**[39]	**ALPHA**[34,35,37]		**PEGASUS**[2]	
Treatment Arm	**Iptacopan**	**Iptacopan**	**Iptacopan**	**C5i**	**Danicopan**	**Danicopan + C5i**	**Placebo + C5i**	**Pegcetacoplan**	**Eculizumab**
Pulmonary oedema	NR	NR	NR	NR	1 (8.3)	NR	NR	NR	NR
Pyelonephritis	NR	NR	1 (1.61)	0	NR	NR	NR	NR	NR
Pyrexia	NR	NR	NR	NR		NR	NR	1 (2.44)	0
Sepsis	NR	NR	0	1 (2.86)	NR	NR	NR	NR	NR
Sinus node dysfunction	NR	NR	1 (1.61)	0	NR	NR	NR	NR	NR
Transient ischemic attack	NR	NR	1 (1.61)	0	NR	NR	NR	NR	NR
Type II diabetes melitus	NR	1 (3)	NR	NR	NR	NR	NR	NR	NR
Urinary tract infection	NR	NR	1 (1.61)	0	NR	NR	NR	NR	NR

* Data from an abstract presenting 75% of the total enrolled population

† Discontinuation due to pregnancy

‡ Thrombotic events experienced also counted as a MAVE

§ Death due to encapsulated bacterial infection

AE: adverse events, BTH: breakthrough hemolysis, C5i: C5 inhibitors, N: total number, n: number, NR: not reported

Table D3.7. Extension Phase Efficacy: Iptacopan and Danicopan

Drug		Iptacopan			Danicopan	
Trial		APPOINT-PNH	APPLY-PNH*[30,33]		ALPHA[†37]	
Treatment Arm		Iptacopan	Iptacopan	C5i-Iptacopan	Danicopan	PBO-Danicopan
Timepoint		48 weeks	48 weeks		24 weeks	
N		40	61	34	41	21
Hemoglobin Level, g/dL	Mean (SD)	NR	12.2 (1.6)	12.1 (1.4)	NR	NR
	Adjusted mean CFB (95%CI)	NR	3.35 (3.0, 3.7)	3.36 (2.9, 3.8)	NR	NR
	Least-squares mean CFB (SE)	NR	NR	NR	3.17 (0.3)	2.26 (0.34)
Increase in Hb ≥2 g/dL from baseline without Transfusions	N (%)	NR	NR	NR	19 (46.3)	7 (35)
	Adjusted mean CFB (95%CI)	NR	NR	NR	NR	NR
	Least-squares mean CFB (SE)	NR	NR	NR	3.17 (0.3)	2.26 (0.3)
Transfusion Avoidance	N (%)	NR	58 (93.5)	32 (94.1)	32 (78)	18 (90)
LDH Level, U/L	Mean (SD)	NR	NR	NR	279.2 (88.6)	227.6 (64.8)
	Adjusted mean CFB (95%CI)	NR	NR	NR	NR	NR
ARC, 10^9 cells/L	Mean (SD)	NR	NR	NR	NR	NR
	Adjusted mean CFB (95%CI)	NR	-106.3 (-117, -94)	-108.0 (-123, -93)	NR	NR
	Least-squares mean CFB (SE)	NR	NR	NR	-80.2 (8.8)	-65.2 (12.7)
FACIT-Fatigue Score	Mean (SD)	NR	NR	NR	40.32 (NR)	40.55 (NR)
	Adjusted mean CFB (95%CI)	NR	9.8 (8.0, 11.6)	10.96 (8.6, 13.3)	NR	NR
	Least-squares mean CFB (SE)	NR	NR	NR	6.12 (1.34)	6.44 (2.47)

95%CI: 95 percent confidence interval, C5I: C5 inhibitors, CFB: change from baseline, LSM: least squares mean, PBO: placebo, SD: standard deviation, SE: standard error

* In the 24-week extension phase, patients in the iptacopan arm continued receiving the drug, those in the C5i arm switched to iptacopan for an additional 24 weeks

† In the 12-week extension phase, patients in the danicopan add-on arm continued receiving danicopan, those in the placebo add-on arm switched to receiving danicopan as add-on for an additional 12 weeks

Table D3.8. Extension Phase Safety: Iptacopan and Danicopan

Drug		Iptacopan			Danicopan	
Trial		APPOINT-PNH[29]	APPLY-PNH*[29,30,33]		ALPHA†[37]	
Treatment Arm		Iptacopan	Iptacopan	C5i-Iptacopan	Danicopan	PBO-Danicopan
Timepoint		48 weeks	48 weeks		24 weeks	
N		40	61	33	80	
Adverse Events, n (%)	Overall	NR	35 (57.4)	21 (63.6)	72 (90)	
	Serious	NR	3 (4.9)	3 (9.1)	2 (2.5)	
	Non-Serious	NR	NR	NR	NR	NR
	Mild	NR	19 (31.1)	15 (45.5)	NR	NR
	Moderate	NR	13 (21.3)	4 (12.1)	NR	NR
	Severe	NR	3 (4.9)	2 (6.1)	NR	NR
Treatment-related Adverse Events, n (%)	Overall	NR	NR	NR	NR	NR
	Serious	NR	NR	NR	NR	NR
Discontinuation, n (%)	Overall	NR	NR	NR	1/48 (1.8)	0
	AE-related	NR	0	0	1/48 (1.8)	0
	Treatment-related	NR	NR	NR	0	0
	BTH-related	NR	NR	NR	0	0
Mortality, n (%)	Overall	NR	0	0	0	0
	AE-related	NR	0	0	0	0
	Treatment-related	NR	0	0	0	0
Adverse Events of Special Interest, n (%)	Breakthrough hemolysis	2 (5.0)	6 (9.8)	1	NR	NR
	MAVEs	NR	2	1	NR	NR
	COVID-19	NR	10 (16.4)	7 (21.2)	NR	NR
	Headache	NR	2 (3.3)	2 (6.1)	NR	NR
	Diarrhea	NR	1 (1.6)	2 (6.1)	NR	NR
	Nasopharyngitis	NR	2 (3.3)	3 (9.1)	NR	NR
	Infections/infestations	NR	2 (3.3)	1 (3.0)	NR	NR

AE: adverse event, BTH: breakthrough hemolysis, C5i: C5 inhibitors, MAVE: major adverse events, n: number, N: total number, NR: not reported, PBO: placebo

* In the 24-week extension phase, patients in the iptacopan arm continued receiving the drug, those in the C5i arm switched to iptacopan for an additional 24 weeks

† In the 12-week extension phase, patients in the danicopan add-on arm continued receiving danicopan, those in the placebo add-on arm switched to receiving danicopan as add-on for an additional 12 weeks

D4. Ongoing Studies

Table D4.1. Ongoing Phase 3 Studies of Iptacopan and Danicopan

Title / Trial Sponsor	Study Design	Patient Population	Primary Outcomes	Estimated Completion
Iptacopan				
Single Arm, Open Label Trial with Iptacopan Treatment for 24 Weeks, in Patients on Stable Regimen of Anti-C5 Who Switch to Iptacopan. (APPULSE) *Novartis Pharmaceuticals* NCT05630001	Phase 3, multicenter, single-arm, open-label trial Estimated enrollment: N = 50 Dosage: Iptacopan 200 mg twice daily	- Adults with a diagnosis of PNH - Stable regimen of anti-C5 antibody treatment for ≥ 6 months pre-screen - Hemoglobin level ≥10 g/dL - Vaccination against Neisseria meningitidis and S. pneumoniae - No prior stem cell or organ transplant	Change from baseline in hemoglobin levels to demonstrate non-inferiority of iptacopan [24 weeks]	January 2025
Long-term Safety and Tolerability of Iptacopan in Patients with Paroxysmal Nocturnal Hemoglobinuria *Novartis Pharmaceuticals* NCT04747613	Phase 3, multicenter, single-arm, open-label, roll-over extension trial Estimated enrollment: N = 250 Dosage: Iptacopan 200 mg twice daily	- Adults with a diagnosis of PNH who completed the extension period of Phase 2 and Phase 3 studies - Vaccination against Neisseria meningitidis and S. pneumoniae - No prior stem cell or organ transplant	Proportion of participants with adverse events [60 months]	June 2026
Danicopan				
A Long-term Safety and Efficacy Study of Danicopan as an Add-on Therapy to Complement Component 5 Inhibitor (C5i) in Participants With PNH *Alexion* NCT05389449	Phase 3, single-arm, long-term extension study Estimated enrollment: N = 100 Dosage: None listed	- Adults who completed an Alexion sponsored clinical study with danicopan as add on to C5i treatment - Vaccination for Neisseria meningitidis	Participants experiencing Treatment-emergent Adverse Events (TEAEs) & Serious TEAEs [3 years]	February 2027

Source: www.ClinicalTrials.gov

C5i: component 5 inhibitor, dL: deciliter, est: estimated, g: grams, mg: milligram, N: total number, PNH: paroxysmal nocturnal hemoglobinuria

D5. Previous Systematic Reviews and Technology Assessments

We identified two ongoing health technology assessments (HTA) of iptacopan and danicopan for the treatment of PNH being conducted by the National Institute for Health and Care Excellence (NICE). We also identified 1 systematic review comparing pegcetacoplan, danicopan added on to eculizumab, and iptacopan to eculizumab alone. All assessments are summarized below.

NICE Technology Assessment for Iptacopan

NICE is conducting a health technology assessment to assess iptacopan for the treatment of PNH (ID6176). The efficacy and safety of iptacopan will be compared to C5 inhibitors eculizumab and ravulizumab, pegcetacoplan, and danicopan as add-on to a C5 inhibitor. The expected publication date is June 12, 2024.

NICE Technology Assessment for Danicopan

NICE is conducting a health technology assessment to evaluate the safety and efficacy of danicopan as add-on treatment to a C5 inhibitor for the treatment of adults with extravascular hemolysis due to PNH (ID5088). Danicopan will be compared to existing C5-inhibitors eculizumab and ravulizumab, pegcetacoplan, and iptacopan. The expected publication date is July 17, 2024.

Syed S, Khan R, Khurram F, et al. Treatment of eculizumab refractory paroxysmal nocturnal hemoglobinuria: A systematic review about current treatment options and future direction. SAGE Open Med. 2023; 11: 1-7.

This systematic review compared the efficacy and safety of available proximal complement inhibitor treatments for eculizumab refractory PNH. Four studies were identified that met inclusion criteria: one Phase 1b and one Phase 3 trial of pegcetacoplan, one Phase 2 trial of add-on danicopan, and one Phase 2 trial of add-on iptacopan. Pegcetacoplan was found to be superior to eculizumab for improvements in hemoglobin level from baseline and normalization of other hematologic laboratory values such as reticulocyte count, LDH, and total bilirubin levels. FACIT-fatigue scores appeared similar in both pegcetacoplan and eculizumab groups. In a Phase 2 trial, danicopan added on to eculizumab was shown to significantly increase hemoglobin levels versus eculizumab alone, decrease the transfusion rate, and increase the FACIT-Fatigue score. The Phase II trial of iptacopan as add-on to eculizumab significantly improved hemoglobin and LDH levels from baseline. All other measured markers of hemolysis such as transfusion avoidance and reticulocyte count were also improved. Overall, all three alternative proximal complement inhibitor therapies to treat PNH resulted in better hemolysis control and fewer sequelae. The advantage of iptacopan and danicopan is the more convenient mode of administration which are oral rather than a subcutaneous injection (pegcetacoplan) or an intravenous infusion (C5 inhibitors).

D6. Heterogeneity and Subgroups

Subgroup results for iptacopan from APPLY-PNH and APPOINT-PNH were discussed in the main report. There were no subgroup data available for danicopan.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1 Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	X	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[72]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[73]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation included treatment-experienced patients with PNH with clinically significant extravascular hemolysis (Table E2).

Table E1.2 Baseline Population Characteristics

	Iptacopan vs. Ravulizumab	Danicopan Add-on vs. Ravulizumab Alone
Mean Age, years	51.0	52.8
Female, %	69.1	62.8
Mean Hgb, g/dL	8.9	7.8
Source	APPLY-PNH trial[41]	ALPHA trial[35]

dL: deciliter, g: grams, Hgb: hemoglobin, LDH: lactate dehydrogenase

E2. Model Inputs and Assumptions

Model Inputs

Discontinuation

We requested this data from the manufacturers but did not receive it. Discontinuation was not available in the limited publicly available data.

Utilities

While the PRINCE trial assessed treatment naïve patients, we chose to use the utility set from this trial instead of the PEGASUS trial which assessed treatment-experienced patients due to several reasons.[57] First, the model based on PRINCE data used a hemoglobin normalization threshold of 12 g/dL compared to 10.5 g/dL based on PEGASUS, which was more closely aligned to the hemoglobin normalization definitions used in APPLY-PNH for iptacopan and ALPHA for danicopan. Given that hemoglobin normalization was the focal point in the way our model was designed, we believed this rationale outweighed the difference in utility values derived from the treatment-experienced versus the treatment-naïve population, given that the primary drivers of utility are expected to be hemoglobin levels and transfusion avoidance. Additionally, the model based on PRINCE data was implemented for the US setting compared to the UK setting for the model based on PEGASUS.

In the manufacturer's cost-effectiveness model for pegcetacoplan using PRINCE data, the threshold for Hgb normalization was ≥12 g/dL. In the absence of additional data from manufacturers, we assume the utility values for pegcetacoplan remain the same for iptacopan and danicopan, even though the threshold for Hgb normalization varies slightly across trials for these drugs.

Economic Inputs

Drug Utilization

The following inputs were used to model drug utilization (Table E3).

Table E2.1 Treatment Regimen Recommended Dosage

Generic Name	Iptacopan	Danicopan	Ravulizumab
Brand Name	NA	NA	Ultomiris®
Manufacturer	Novartis	Alexion	Alexion
Route of Administration	Oral	Oral	IV
Dosing	200 mg twice daily	150-200 mg three times daily	Loading dose: weight-based Maintenance dose: once every eight weeks starting two weeks after loading dose

Mg: milligram, NA: not available

Health Care Utilization Costs

Table E4. details the non-drug costs that were used in our model.

Table E2.2 Non-Drug Costs

		Value	Source
IV Administration Cost (First Hour)		132.16	CMS Fee Schedule
IV Administration Cost (Subsequent Hours)		28.47	CMS Fee Schedule
Monitoring			
	Hematologist Visit per Cycle – Hgb Normalized and Not Normalized	1	Fishman et al. 2023
	Hematologist Visit per Cycle – Transfusion Required	13	
	Hematologist Visit Vost	$143.34	CMS Fee Schedule
Blood Tests			
	Blood Tests per Cycle – Hgb Normalized and Not Normalized	2	Fisman et al. 2023
	Blood Tests per Cycle – Transfusion Required	4	
	Blood Test Cost	$9.15	CMS Fee Schedule
Blood Transfusions			
	Total Number – Initial	2.65	Fishman et al. 2023
	Increment per Cycle for Those Who Stay in Transfusion Required State	0.2	
	Maximum Number in One Cycle	8.17	
	Blood Transfusion Cost	$2772	Cheng et al. 2021[74]

Hgb: hemoglobin, IV: intravenous

Modified Societal Perspective Costs

Available data from the literature was limited for the modified societal perspective. One source measured productivity costs related to the time commitments required for intravenous administration of ravulizumab at infusion clinics.[75] These included travel time, wait time, infusion

time for loading and maintenance doses, and recovery time for a total of 330 minutes. The annual productivity cost per treated patient with ravulizumab was estimated to be $2,523. We used another study to estimate annual PNH-related absenteeism costs for hospitalization and ER-related events based on whether patients were transfusion free ($108) or transfusion dependent ($1,810).[74]

E3. Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Figures E3.1. and E3.2. present the results from the one-way sensitivity analysis from the health care sector perspective for both iptacopan and add-on danicopan, respectively. Tables E3.1. and E3.2. present the lower and upper incremental cost-effectiveness ratios based on the lower and upper limit inputs for the most influential parameters.

Figure E.1. Tornado Diagram for Iptacopan

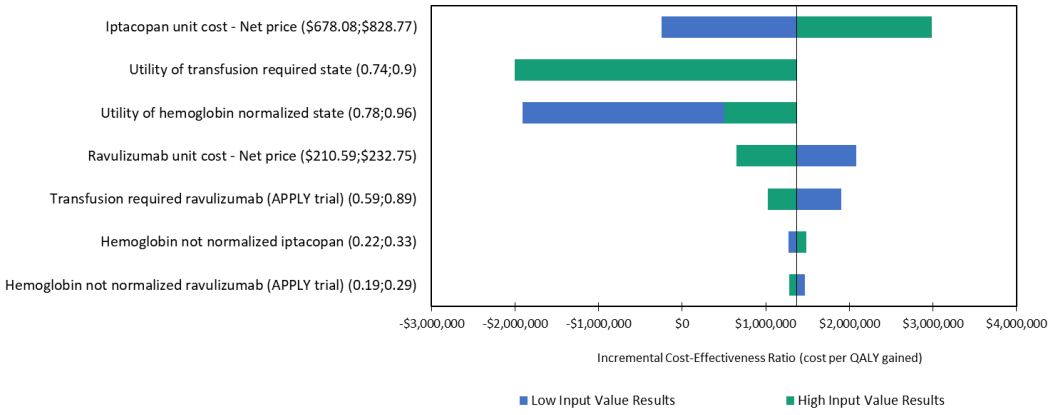


Table E3.1 Tornado Diagram Inputs and Results for Iptacopan Versus **Ravulizumab**

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Iptacopan Unit Cost	-248,000	2,983,000	678	829
Utility of Transfusion Required State	-2,002,000	510,000	0.74	0.90
Utility of Hemoglobin Normalized State	-1,913,000	504,000	0.78	0.96
Ravulizumab Unit Cost	653,000	2,082,000	211	233
Transfusion Required, Ravulizumab (APPLY trial)	1,027,000	1,902,000	0.59	0.89
Hemoglobin Not Normalized, Iptacopan	1,269,000	1,483,000	0.22	0.33
Hemoglobin Not Normalized, Ravulizuamb (APPLY Trial)	1,279,000	1,470,000	0.19	0.29

CE: cost-effectiveness

*Note lower input may reflect either upper or lower Incremental Cost-Effectiveness Ratio value depending on the direction that the input has on the Incremental CE Ratio output.

Figure E.2. Tornado Diagram for Add-on Danicopan

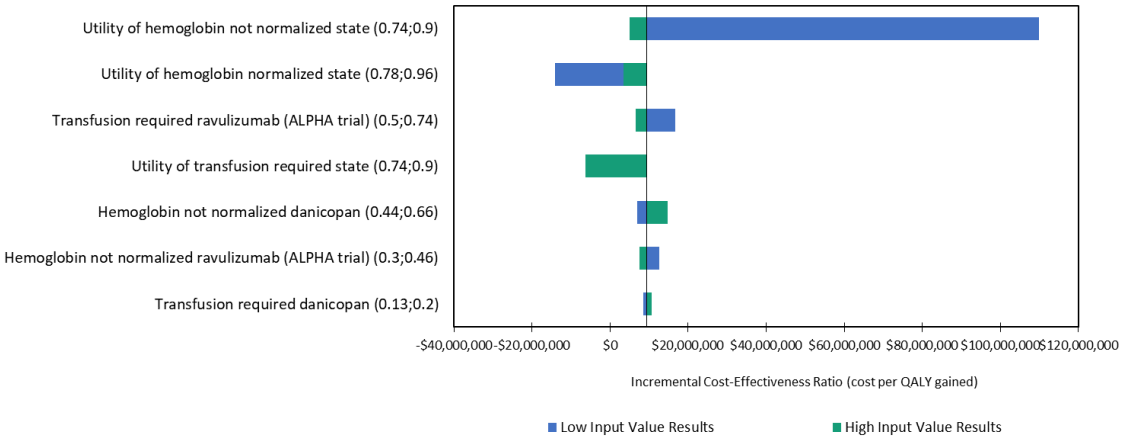


Table E3.2 Tornado Diagram Inputs and Results for Add-on Danicopan versus Ravulizumab

	Lower Incremental CE Ratio	Upper Incremental CE Ratio	Lower Input*	Upper Input*
Utility of Hemoglobin Not Normalized State	4,941,000	109,900,000	0.74	0.90
Utility of Hemoglobin Normalized State	-14,143,000	3,544,000	0.78	0.96
Transfusion Required, Ravulizumab (ALPHA trial)	6,486,000	16,803,000	0.50	0.74
Utility of Transfusion Required State	-6,379,000	2,716,000	0.74	0.90
Hemoglobin Not Normalized, Danicopan	6,954,000	14,776,000	0.44	0.66
Hemoglobin Not Normalized, Ravulizumab (ALPHA trial)	7,562,000	12,622,000	0.30	0.46
Transfusion Required, Danicopan	8,433,000	10,747,000	0.13	0.20

CE: cost-effectiveness

*Note lower input may reflect either upper or lower Incremental Cost-Effectiveness Ratio value depending on the direction that the input has on the Incremental CE Ratio output.

E4. Scenario Analyses

We conducted several scenario analyses to examine uncertainty and potential variation in the findings. Of note, in Scenario 5, we assumed the cost-offsets by treating patients with iptacopan were capped at $150,000. This scenario was not applied to the add-on danicopan comparison to ravulizumab alone as the cost-offsets never exceeded $150,000 annually. The scenario analysis results as total outcomes and incremental cost-effectiveness ratios are presented in Tables E4.1 And E4.2.

Table E4.1 Scenario Analysis Results (Total Outcomes)

	Drug Cost	Total Cost	QALYs	Life years	evLYs
Scenario 1: Modified societal perspective					
Iptacopan	$2,360,000	$2,376,000	3.65	4.29	3.65
Ravulizumab	$2,088,000	$2,192,000	3.50	4.29	3.50
Danicopan + Ravulizumab	$2,712,000*	$2,750,000*	3.51	4.26	3.51
Ravulizumab	$2,073,000	$2,160,000	3.45	4.26	3.45
Scenario 2: Lifetime time horizon					
Iptacopan	$8,356,000	$8,414,000	12.79	15.19	12.79
Ravulizumab	$7,393,000	$7,885,000	12.45	15.42	12.45
Danicopan + Ravulizumab	$9,175,000*	$9,296,000*	11.96	14.57	11.96
Ravulizumab	$6,990,000*	$7,369,000	11.74	14.57	11.74
Scenario 3: Utility values from PEGASUS					
Iptacopan	$2,360,000	$2,375,000	3.35	4.29	3.35
Ravulizumab	$2,088,000	$2,175,000	3.02	4.29	3.02
Danicopan + Ravulizumab	$2,712,000*	$2,737,000*	3.16	4.26	3.16
Ravulizumab	$2,073,000	$2,144,000	2.99	4.26	2.99
Scenario 4: Assuming a BTH of 17.14% for Ravulizumab in Iptacopan Comparison					
Iptacopan	$2,360,000	$2,375,000*	3.65	4.29	3.65
Ravulizumab	$2,088,000	$2,192,000	3.50	4.29	3.50
Scenario 5: $150,000 Cost-offset Cap					
Iptacopan	$2,360,000	$2,375,000	3.65	4.29	3.65
Ravulizumab	--$677,000	$765,000	3.50	4.29	3.50

*based on placeholder price

evLY: equal-value of life-year, QALY: quality-adjusted life-year

Table E4.2 Scenario Analysis Results (Incremental Cost-Effectiveness Ratios)

Treatment	Comparator	Cost per QALY gained*	Cost per life years gained*	Cost per evLY gained*
Scenario 1: Modified societal perspective				
Iptacopan	Ravulizumab	$1,258,000	--†	$1,258,000
Danicopan + Ravulizumab	Ravulizumab	$9,405,000	--±	$9,405,000
Scenario 2: Lifetime time horizon				
Iptacopan	Ravulizumab	$1,575,000	More costly, less effective	$1,575,000
Danicopan + Ravulizumab	Ravulizumab	$9,023,000	--±	$9,023,000
Scenario 3: Utility values from PEGASUS				
Iptacopan	Ravulizumab	$605,000	--†	$605,000
Danicopan + Ravulizumab	Ravulizumab	$3,572,000	--±	$3,572,000
Scenario 4: BTH of 17.14% for Ravulizumab in Iptacopan Comparison				
Iptacopan	Ravulizumab	$1,247,000	--†	$1,247,000
Scenario 5: $150,000 Cost-offset Cap				
Iptacopan	Ravulizumab	$11,022,000	--†	$11,022,000

*based on placeholder price

†Not calculable due to assumed equivalence in life-years (difference of <0.01)

±Not calculable due to equivalence in life-years

evLY: equal-value of life-year, QALY: quality-adjusted life-year

E5. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. As part of ICER's efforts in acknowledging modeling transparency, we shared the model with the relevant manufacturer for external verification around the time of publishing the draft report for this review.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with iptacopan and danicopan. In alignment with the cost-effectiveness analysis, the eligible population for iptacopan and danicopan is for patients who are treatment-experienced with clinically significant extravascular hemolysis. To estimate the size of the potential candidate population we used inputs for the US population size (344,207,840),[61] the prevalence of PNH (12.5 cases per 1,000,000; 0.0000125%),[62] the percentage of patients with PNH who are symptomatic and eligible for a C5i (61.3%, assuming that the percentage of patients who are symptomatic are those with a history of RBC transfusions),[6] and the percentage of patients (21%) that are not controlled on current therapy (i.e., experience a clinically significant extravascular hemolysis and would be eligible to switch to iptacopan or danicopan as an add-on therapy).[63] Applying these sources results in estimates of 554 treatment experienced patients in the US over five years. Given we are assessing two new market entrants for the prevalent population, we assumed that 50% of patients each year will initiate iptacopan and the remaining 50% of patients will initiate danicopan (added on to standard of care, i.e., ravulizumab). We recognize that there may be differential uptake between iptacopan and danicopan in practice. Our objective is intended to provide a framework in which decision-makers and policymakers can then apply their own assumptions that align with their context. Applying these sources results in estimates of 277 eligible patients in the US for iptacopan, and 277 eligible patients in the US for danicopan. For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 55 patients per year for iptacopan and 55 patients per year for danicopan. Our analysis is focused on patients who are treatment experienced and, consequently, represents an underestimate of the potentially eligible patient population if iptacopan is used for patients who are treatment naïve.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[76,77] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.

G. Supplemental Policy Recommendations

Payers

Recommendation 1

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: **https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf**

Drug-Specific Considerations

Although PNH is a rare disease, the need for indefinite therapy to manage the illness and the high annual prices for existing and newer treatments, may lead payers to develop prior authorization criteria and to consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right. To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for oral iptacopan and add-on danicopan.

Coverage Criteria for Iptacopan

- **Age:** Age criteria, if given, will likely follow the FDA label in line with clinical trial eligibility criteria. There are no ongoing clinical trials in pediatric populations. However, payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: If payers are considering establishing clinical eligibility criteria for coverage beyond that specified in the FDA label, they will look to any existing clinical guidelines and to the eligibility criteria for the pivotal trial(s). For treatments of PNH, however, there are no established clinical guidelines, and payers may find no benefit in strictly applying pivotal trial eligibility criteria since the inclusion criteria focus on laboratory markers of hemolysis with minor variations across trials that experts consider to be

meaningless differences. Experts also advised that there is no clear consensus on how to operationalize a definition of "clinically significant" extravascular hemolysis. Experts largely recommend treatment for patients with symptomatic PNH or those without symptoms but have a sufficiently large PNH clone size (e.g., ≥50%), which indicates a greater risk for thrombosis and hemolytic anemia. The severity of PNH can vary substantially over time and, from a patient's perspective, can include a combination of fatigue, symptoms from smooth muscle dysfunction (i.e., abdominal pain), burden from red blood cell transfusions, and major adverse vascular events, such as thromboses. Clinical attestation alone may be sufficient to identify clinically eligible patients.

- **Exclusion criteria**: It is reasonable to exclude patients with bone marrow failure as determined by prior history or absolute reticulocyte counts since complement inhibitors would not be expected to improve anemia in these situations. However, payers may similarly find no benefit in strictly applying this criterion from clinical trials since there were minor variations in the reticulocyte count cutoff used as a proxy of bone marrow failure.

- **Provider restrictions**: Patients and clinical experts agreed that it is reasonable to restrict prescriptions to hematologists.

Coverage Criteria for Danicopan add-on – Assuming FDA Approval

- **Age:** Age criteria, if given, will likely follow the FDA label in line with clinical trial eligibility criteria. There are no ongoing clinical trials in pediatric populations. However, payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: Experts would consider adding on danicopan if patients developed cs-EVH despite a stable regimen of a C5 inhibitor (defined as at least 6 months in the ALPHA trial) to improve hemoglobin and quality of life and to decrease transfusion dependence. However, payers may find no benefit in strictly applying pivotal trial eligibility criteria since the inclusion criteria largely focus on laboratory markers of EVH with minor variations between trials for proximal complement inhibitors studied in this subpopulation without stipulating symptoms or transfusion dependence. Although it was not required for inclusion in the pivotal trial, payers might consider a history of red blood cell transfusion within the prior 6 months as a criterion of clinically significant EVH since all participants in the ALPHA trial had received at least one transfusion.

- **Exclusion criteria**: It is reasonable to consider bone marrow failure as an exclusion criterion since complement inhibitors would not be expected to improve anemia in this setting. However, payers may find no benefit in applying a single criterion used in pivotal trials, since

there were minor variations in the reticulocyte count cutpoint used as a proxy of bone marrow failure.

- **Provider restrictions**: Patients and clinical experts agreed that it is reasonable to restrict prescriptions to hematologists.

Step Therapy

Payers should allow patients and clinicians to choose from multiple options until there is greater certainty about long-term safety, durability, and comparative effectiveness to inform practice.

The lack of evidence to distinguish overall clinical outcomes between iptacopan and C5 inhibitors, along with the lack of clinical characteristics or biomarkers to help predict response, raise the possibility that payers will consider step therapy through a preferred option for patients beginning treatment. However, for treatment-naïve patients, clinical experts and patients argued that C5 inhibitors are seen as frontline therapy, and active utilization management has been very limited for PNH. Clinical experts and patients emphasize the importance of maintaining the ability to tailor treatment options given the important trade-offs involved between selecting older, more proven IV options and newer oral options. Any approach to step therapy would also need to be sensitive to socio-economic elements that may create important benefits for certain patients to take one option or the other.

In regard to danicopan, for treatment-experienced PNH patients who develop cs-EVH on a stable C5 inhibitor regimen, clinical experts do not know which patients could be safely switched to pegcetacoplan or iptacopan monotherapy versus which patients should add on danicopan to a C5 inhibitor to ensure durable control of the most severe disease manifestations from uncontrolled terminal complement activation. Danicopan will only be used as an add-on to C5 inhibitor treatment, so there is likely going to be no interest among payers in considering a step therapy approach that would force patients to switch from C5 treatment to pegcetacoplan or iptacopan as an alternative to adding danicopan. While patients may do fine switching to pegcetacoplan or iptacopan monotherapy, experts expressed uncertainty about which patients would require dual proximal and terminal complement inhibition to adequately control their illness. However, there is no doubt that adding danicopan to C5 inhibitor treatment would create a much more expensive regimen than monotherapy with pegcetacoplan or iptacopan. Given the current state of the evidence, clinical experts felt it would be reasonable for payers to consider contacting clinicians requesting danicopan to ensure that they are aware of these other treatment options, particularly that of iptacopan, which would allow patients to try an oral regimen. However, as noted earlier, active utilization management has been very limited for PNH, and clinical experts and patients emphasize the importance of maintaining the ability to tailor treatment options given the important trade-offs involved between selecting older, more proven IV options and newer oral options.

H. Public Comments

This section includes summaries of the public comments prepared for the Public Meeting on Friday, February 16th, 2024. . These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Both speakers submitted summaries of their public comments.

A video recording of all comments can be found here, beginning at minute 00:09. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Anita Hill, MD, PhD, Alexion, AstraZeneca Rare Disease
Vice President, Hematology and Nephrology TA Lead

We appreciate the opportunity to participate in ICER's public meeting to discuss treatments for paroxysmal nocturnal hemoglobinuria (PNH). Alexion, AstraZeneca Rare Disease has been a pioneer in complement biology for more than 30 years, serving patients and families affected by rare diseases and devastating conditions – including those living with PNH - through the discovery and development of life-changing medicines.

There are unique considerations that must be kept in mind when discussing the value of medicines for rare diseases. Rare diseases tend to be highly heterogeneous with diverse patient symptomatology, making diagnosis challenging: on average, it takes a rare disease patient 4.8 years and 7.3 specialists to receive an accurate diagnosis. It also makes measuring and adequately capturing the full treatment impact challenging, making generalized, population-based predictions less meaningful.

PNH is **much more** than a disease of anemia and hemoglobin. PNH is a rare, chronic, potentially life-threatening disease of uncontrolled terminal complement activation leading to intravascular hemolysis (IVH), thrombosis, organ damage, and pre-mature mortality. The prevalence of PNH is estimated to be 12 to 13 patients per 1,000,000 in the general population.[1]

Alexion transformed the natural history of PNH over the past two decades with the advent of C5 inhibitors, first with eculizumab and then building upon that foundation with ravulizumab (ULTOMIRIS). Today, ravulizumab is the standard of care in PNH in the United States due to its effectiveness in controlling the critical underlying pathophysiologic process, terminal complement activity and **intravascular** hemolysis. Ravulizumab, with its improved pharmacokinetics, provides immediate, complete, and sustained terminal complement inhibition compared to eculizumab. This inhibition results in control of IVH, reduction in thrombosis risk, and extended patient survival, to 97.5% over six years of follow-up.[2,3] The **sustained and targeted** inhibition of **terminal** complement activity should never be compromised. Intravascular breakthrough hemolysis needs to be avoided – both in rate and severity.

In addition to the important results already mentioned, compared to eculizumab, ravulizumab only needs to be administered every eight weeks for adults following an initial loading dose and achieves that important complete and sustained terminal complement inhibition with that dosing schedule. Use of ravulizumab demonstrated reduction in overall resource use and is cost saving for patients with PNH.[4]

Approximately 10%-20% of patients with PNH experience clinically significant extravascular hemolysis (cs-EVH) while treated with C5 inhibitor due to C3 deposition, which may impact quality of life. Importantly, EVH does not impact survival in this disease. The significant morbidity and mortality in PNH is a result of terminal complement activity and IVH. With this in mind, Alexion developed danicopan, a first-in-class, oral, factor D inhibitor that targets the complement alternative pathway activity.

The ALPHA trial is a phase 3 **double blind, placebo controlled clinical trial** (*not* an open label study) designed to evaluate the efficacy and safety of danicopan vs. placebo as an add-on treatment to ravulizumab or eculizumab in PNH patients living with cs-EVH. Danicopan demonstrated statistically and clinically significant improvement in hemoglobin, 2.94 g/dL vs. 0.5 g/dL, P<0.0001, which may result in significant improvements in FACIT-Fatigue scores which is clinically meaningful for patients.[5] Results showed that 83% of patients treated with danicopan did not need transfusion through week 12, which is a significant improvement over the comparator arm.[5]

Danicopan improved hemoglobin and reduced the need for transfusion by addressing the cs-EVH while **importantly** maintaining control of IVH. As ICER noted in its revised evidence report, danicopan as an add-on to ravulizumab or eculizumab offers the *"dual protection against both intra and extravascular hemolysis plus the greater certainty of protection against thrombosis."* Additionally, danicopan demonstrated a favorable benefit-risk profile including in the Long-Term Extension period.

Patients with rare diseases are the most marginalized communities and these innovations are immensely meaningful to them and their families' lived experiences. We are proud to have contributed to the PNH community for over two decades by bringing innovative and impactful medicines to patients. We're also incredibly excited about danicopan, which if approved in the US, will be an important and meaningful addition for the management of cs-EVH in a sub-population of patients with PNH treated with ravulizumab or eculizumab.

Importantly, with danicopan as an add-on to those therapies, what is key for patients is that the terminal complement inhibition is not compromised. In addition, the long-term benefits for patients, such as reduction in thrombosis and improved survival that have been demonstrated with ravulizumab, may continue.

We remain steadfast in our commitment to serving patients living with PNH.

References

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3 Kulasekararaj A, et al. Abstract P772 presented at European Hematology Association, EHA2023 Congress.; June 8 - 15; Frankfurt, Germany.

4 Tomazos I, et al. Hematology. 2020;25(1):327-334.

5 Lee JW, et all. Lancet Haematol. 2023; 10: e955–65.

Dr. Hill is a full-time employee at Alexion.

Evan Rossman
Onboarding Specialist/Solution Expert

My name is Evan Rossman and I am currently 29 years old and have been living with PNH for around 3 years. I live in NYC and was diagnosed after my coloring looked concerning to my parents and I was asked to get bloodwork done.

The bloodwork found my hemoglobin was 5.5 and then testing began. After a week, my hematologist at the time thought PNH might be the cause, especially due to my leg hurting from an injury I believed to be an ankle sprain from biking. After that 2 blood clots were found in my leg and PNH diagnosis came. Then treatment and blood transfusions began.

I currently get treatment every 8 weeks and plan my entire work, social, and personal life around that schedule. PNH did not directly affect my physical health as a symptom but my mental health took a toll due to the diagnosis of the disease. I now advocate for the disease and want to spread awareness to others. My quality of life has been affected of course but this disease for me has really taught me how to focus on time management. Understanding time and energy management for all the other events in life I want to attend and the goals I want to achieve both personally and professionally have become really important. Time and energy management are due to the duration and of my treatment schedule plus with the ongoing symptoms of the disease.

I am currently very open to changing treatments and looking into other drugs in order to make my way of life easier. Obviously, what comes into account is cost of the drug and safety concerns. Due to my current insurance and treatment plan it is very difficult for me to change where and when I get my treatment, it would be an entire process to make any changes.

I want to thank everyone who is involved with this process and for helping improve the lives of everyone affected with PNH.

Thank you,
Evan Rossman

No conflicts to disclose.

I. Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the Friday, February 16, 2024 public meeting of Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria.

Table I1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Foluso Agboola, MBBS, MPH, Vice President of Research, ICER	**Josh Carlson, PhD, MPH**, Professor, Department of Pharmacy, University of Washington
Sarah Emond, MPP, President and CEO, ICER	**Grace Ham, BS**, Program and Events Coordinator, ICER
Belen Herce-Hagiwara, BA, Senior Research Assistant, ICER	**Anil Makam, MD, MAS**, Assistant Professor of Medicine, University of California San Francisco
Shahariar Mohammed Fahim, PhD, Research Lead, Evidence Synthesis, ICER	**Steven Pearson, MD, MSc**, Special Advisor, ICER
Becca Piltch, MPP, Program Manager, ICER	**Marina Richardson, PhD, MSc,** Senior Health Economist, ICER
Kangho Suh, PharmD, PhD, Assistant Professor, School of Pharmacy, University of Pittsburgh	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF*	
Ralph Brindis, MD, MPH, MACC, FSCAI, FAHA, Clinical Professor of Medicine, UCSF	Felicia Cohn, PhD, HEC-C, Bioethics Director, Kaiser Permanente Orange County/ University of California Irvine School of Medicine
Robert Collyar, Patient Advocate, Breast Cancer; Board Member, Breast Cancer Action; Co-Founder, Clinical Trials Information Project	Rena Fox, MD, Professor of Medicine, UCSF
Kim Gregory, MD, MPH, Vice Chair Department OB GYN, Cedars Sinai Medical Center	**Paul Heidenreich, MD**, Professor of Medicine, Stanford University
Annette Langer-Gould, MD, PhD, Regional Lead, Translational Neuroscience, Southern California Permanente Medical Group/Kaiser Permanente	Sei Lee, MD, MAS, Associate Professor of Medicine, UCSF
Joy Melnikow, MD, MPH, Associate Professor, UCLA	Kathryn Phillips, PhD, Professor, UCSF
Ann Raldow, MD, MPH, Associate Professor, UCLA	**Tony Sowry, BA**, Patient Advocate and Lead Volunteer, National Patient Advocate Foundation
Joanna Smith, LCSW, MPH, Healthcare Advocate	

*No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table I3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Leigh Clark, BCPA, Director, Patient Services, Aplastic Anemia and MDS International Foundation	AAMDSIF has received <25% of funding from health care companies.
Eve Hindin, PharmD, MS, Executive Director, Clinical Formulary, CVS Health	Dr. Hindin is a full-time employee at CVS Health.
Jeri Keiller, Certified Public Accountant	No conflicts to disclose.
Irina Murakhovskaya, MD, Associate Professor, Albert Einstein College of Medicine, and Montefiore Medical Center	Dr. Murakhovskaya has received more than $5,000 in honoraria or consulting fees from Novartis and Alexion. Dr. Murakhovskaya has also received >25% of funding from WAIHA Warriors and has served as the Principal Investigator for the Novartis CLNP023C12303 trial.
Caroline Piatek, MD, Associate Professor of Clinical Medicine, University of Southern California	Dr. Piatek has received more than $5,000 in honoraria or consulting fees from Argenx, Omeros, Janssen, Novartis, AstraZeneca/Alexion, Rigel, Apellis, Sanofi, Sobi. Dr. Piatek has also received manufacturer support through AstraZeneca/Alexion, Apellis.
Emily Tsiao, PharmD, BCPS, Clinical Pharmacist of Medical Policies, Premera	Dr. Tsiao is a full-time employee at Premera.