

**Aplastic Anemia and MDS International Foundation Comments
on ICER Assessment of Iptacopan and Danicopan – August 14, 2023**

The Aplastic Anemia and MDS International Foundation (AAMDSIF) supports the development of more treatment options for patients with paroxysmal nocturnal hemoglobinuria (PNH). The symptoms experienced by these patients impact their quality of life and they deserve access to drugs that are safe and effective.

Through our educational conferences, webinars, support groups, and individualized assistance, AAMDSIF interacts daily with PNH patients, and we understand how managing this chronic, lifelong disease affects their daily lives and the lives of their caregivers. These patients experience symptoms resulting from PNH such as hemolysis, thrombosis, and low blood cell levels. Patients with PNH may also suffer from possible side effects of treatment, including dizziness and headaches, gastrointestinal pain, lower back pain, and infection.

AAMDSIF supports investment in research to foster innovative approaches to drug development and more therapeutic choices for patients. Additional treatment options would enable patients to work with their health care team to determine the best disease management course for their individual situation, including quality of life considerations. This would address the specific condition of the patient and enhance treatment adherence.

PNH patients face a lifetime of managing this rare disease and they deserve accessible, effective therapies that meet their needs.

Alexion appreciates the opportunity to comment on ICER's *Draft Scoping Document for Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria (PNH)*.

As a leader in rare diseases for more than 30 years, Alexion is focused on serving patients and families affected by rare diseases and devastating conditions, including PNH, through the discovery, development, and commercialization of life-changing medicines. We believe that danicopan will, pending regulatory approval, be an important and meaningful addition to the management of clinically significant extravascular hemolysis (cs-EVH) in a sub-population of patients with PNH treated with C5 inhibitors. Alexion remains steadfast in our commitment to ensuring that people living with PNH have access to novel medicines that address the unmet needs of this patient population.

As ICER embarks on this review, we would like to raise five critical points that we urge ICER to consider, not only in the scoping document, but throughout the entire evaluation.

1. ICER should further distinguish the cs-EVH population from the overall PNH population to ensure appropriate assessment of danicopan.

While the Draft Scoping Document states that danicopan is expected to be used as add-on therapy to C5 inhibitors for patients with cs-EVH, cs-EVH is not clearly characterized and sufficiently differentiated from intravascular hemolysis (IVH). IVH leads to life threatening consequences, such as thrombosis and end-organ damage.¹ Ravulizumab and eculizumab have demonstrated transformative, long-term benefits in controlling terminal complement activity, and thereby IVH, in patients with PNH. A small subset of PNH patients (10% – 20%) may develop cs-EVH.^{2,3} EVH, the removal of red blood cells outside of the blood vessels, can sometimes occur in PNH patients who are treated with C5 inhibitors.^{4,5} Since C5 inhibition enables PNH red blood cells to survive and circulate, EVH may occur when these now surviving PNH red blood cells are marked by proteins in the complement system for removal by the spleen and liver.^{4,6,7,8,9} Patients with cs-EVH may experience persistent symptomatic anemia, chronic blood transfusions, and fatigue.^{10,11} Pending approval, danicopan will expand on the benefits of C5 inhibitor therapy by inhibiting Factor D and preventing downstream activation of C3, providing EVH control for the subset of patients who experience signs and symptoms of cs-EVH.¹²

2. It is inappropriate to assess danicopan under ICER's current scope, where the population of interest includes all patients with PNH. ICER should clearly define the subset of the broader PNH population that danicopan is intended to treat within the population section of the PICOTS criteria.

As previously mentioned, given that danicopan is designed to treat a specific subset of PNH patients treated with C5 inhibitors with cs-EVH, it is important to assess danicopan within the most clinically appropriate population. Clinical trials for danicopan include patients with diagnosed PNH with cs-EVH and at least 6 months of C5 inhibitor therapy prior to treatment initiation.⁷ These are not patients that are naïve to any complement inhibitors. Therefore, any comparisons made outside of this population may result in misinterpretation of the treatment effect of danicopan and we would caution against drawing any meaningful conclusions about danicopan's clinical effectiveness based on those comparisons. ICER should clearly distinguish between the specific populations that danicopan and iptacopan intend to treat within the population section of the PICOTS criteria of the scoping document and throughout the entire evaluation.

3. It is important to acknowledge the well-established efficacy and safety of ravulizumab and eculizumab across numerous disease signs and symptoms, as well as the availability of long-term efficacy and safety data.

PNH is an ultra-rare, chronic, life-threatening disease of uncontrolled terminal complement activation leading to 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.¹³ The advent of the C5 inhibitors, ravulizumab (ULTOMIRIS) and eculizumab (SOLIRIS), has transformed the natural history of PNH and patient survival has been significantly extended, leading to a survival rate of >95% over 4-years of follow-up.¹⁴ As such, ravulizumab and eculizumab can be considered the SOC for PNH and are the backbone therapy for danicopan.

Ravulizumab has demonstrated efficacy across various endpoints and time periods and is considered an effective and safe therapy to treat patients with PNH over a long-term period. Treatment with ravulizumab controls terminal complement activation and significantly reduces IVH, reducing the risk of thrombosis, improving overall survival and quality of life. The clinical safety and efficacy of ravulizumab has been observed in two phase III clinical studies and has reported 1-year and 2-year data.^{15,16} It has demonstrated clinical benefit in transfusion avoidance and lactate dehydrogenase (LDH) normalization, along with benefits in fatigue, breakthrough intravascular hemolysis, and hemoglobin stabilization. Ravulizumab has also established long-term efficacy and safety with up to 6 years of data, demonstrating long-term benefits in IVH control, transfusion avoidance, fatigue, breakthrough intravascular hemolysis, reduced thrombosis, and improved survival.^{17,18}

Compared to eculizumab, ravulizumab offers a more convenient weight-based dosing regimen, given its longer half-life, and provides immediate, complete, and sustained inhibition of terminal complement activity. It is administered as an intravenous infusion every 8 weeks for adults or every 4 weeks for children, following an initial loading dose. This dosing schedule, along with improved quality of life, can confer significant benefits to patients – in fact, 9 out of 10 patients prefer ravulizumab over eculizumab.^{19,20} Furthermore, ravulizumab has demonstrated reduction in overall resource use and was found to be cost-saving for patients with PNH.²¹ At this time, ravulizumab represents >80% of the C5 inhibitor therapy used among patients with PNH who are currently being treated,²² and conclusions from ICER's evaluation in PNH should reflect that ravulizumab is the SOC in PNH.

- 4. We appreciate ICER's recognition of patient-relevant endpoints with the inclusion of fatigue and HRQoL. However, to ensure all aspects of the disease are appropriately represented, ICER should prioritize the patient-centered, life-threatening outcomes of thrombotic events, mortality, breakthrough intravascular hemolysis, and IVH as key clinical outcomes of interest, as well as clarify the intent to evaluate 'hematologic response', which is a recently described²³ and not yet widely used or accepted term in PNH.²⁴**

Certainly, the outcomes included in the PICOTS criteria are relevant to the assessment of PNH; however, some of these outcomes are less relevant to danicopan's target population of patients with cs-EVH treated with C5 inhibitors. As such, we request ICER place emphasis on IVH (based on LDH levels), breakthrough intravascular hemolysis, and thrombotic events, as these are highly relevant consequences of the disease for patients with PNH. Managing breakthrough intravascular hemolysis is more critical to address potential life-threatening outcomes, particularly risk of thrombosis. Therefore, it is important to distinguish between IVH and EVH in the context of breakthrough hemolysis, particularly for the assessment of danicopan, which is intended to specifically address signs and symptoms of cs-EVH.

Furthermore, "hematologic response" should also be clearly defined within the scoping document and throughout the evaluation to ensure accurate interpretation of findings. Previously published articles^{25,26,27,28} have assessed hemolysis by LDH levels, rather than hemoglobin. LDH ≥ 1.5 x upper limit of normal is the threshold for increased thrombotic risk and increased mortality²⁵ and LDH is the critical marker for other serious manifestations and outcomes in PNH, including fatigue.¹⁷ ICER should use the same definition in order to closely align with current literature.²⁴

5. **Finally, we would like to reiterate our concerns regarding the application of ICER's framework in rare and ultra-rare diseases.**

We believe that ICER's framework is inadequate to assess the value of medicines that address the life-long disease impact and burdensome journey that people with rare and ultra-rare diseases, such as PNH, experience.

- **Population-based predictions could be misleading when dealing with highly heterogeneous diseases.** Ultra-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.^{29,30} It also makes measuring and adequately capturing the full treatment impact challenging, making generalized, population-based predictions less meaningful.
- **Patient and caregiver perspectives are crucial, yet they are not taken into consideration in the current framework.** With appropriate targeted treatments, patients with PNH can reclaim control over their lives, allowing themselves and caregivers to be fully present, and look forward to significant family, social, and professional milestones^{31,32} – aspects that are meaningful to patients in ways economic modeling cannot evaluate. ICER's current framework is too narrowly focused on capturing economic value while undervaluing the meaningfulness of a new treatment for patients with serious and life-threatening rare diseases and their caregivers. Without consideration of the arduous patient journey for patients living with PNH, results from ICER's assessment may be misinterpreted and misused and could limit patients' access to novel medicines that can improve their lives. Additional patient and caregiver perspectives, including rare disease patient representatives on ICER's team of evaluators, should be included in ICER's value framework to more accurately capture the patient experience.
- **Real-world evidence is not explicitly included in the comparative effectiveness analysis.** Long-term safety and efficacy data and real-world data are rarely considered in traditional value frameworks, as they can be difficult to evaluate. However, these offer critical insights in evaluating the value interventions bring forward to patients and may limit the interpretation of ICER's results. The complexity of incorporating long-term data and real-world data is further exacerbated in rare and ultra-rare conditions, as real-world data can be difficult to collect, given the rarity and highly disparate and specialized nature of treatment. While complexities are appreciated, they are still a substantial gap in the framework and impact the understanding of treatment value.
- **Conventional cost-effectiveness analysis (CEA) approaches discourage further investment in innovative medicines for ultra-rare and orphan diseases.** The unmet need in rare diseases continues to be significant. There are more than 400 million people around the world who are affected by a rare disease, half of whom are children.³³ More than 95% of rare diseases lack an approved treatment option.³⁴ Therefore, sustained investment in rare diseases is critical to addressing these patients' needs. Conventional CEA undervalues rare disease medicines, which can discourage scientific progress and investments, along with the hope for a better future that innovative therapies may bring. Alexion has invested in numerous clinical programs with this hope to meet patients' needs, realizing that some of these programs may not be successful.

Alexion remains steadfast in our commitment to ensuring patient access to danicopan and our portfolio of treatment options that serve PNH patients. We thank you for your time and consideration in hearing the Alexion perspectives on danicopan and PNH broadly. We trust that this committee's work will move forward in a clinically appropriate manner that protects the best interests of often underserved patients impacted by ultra-rare and orphan diseases.

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August 14, 2023

Re: Apellis comments on ICER's PNH Draft Scoping Document

Apellis appreciates the opportunity to provide comments on ICER's paroxysmal nocturnal hemoglobinuria (PNH) draft scoping document. EMPAVELI[®] (pegcetacoplan) is a targeted C3 inhibitor indicated for the treatment of adult patients with PNH, a rare, chronic, life-threatening blood disorder characterized by the destruction of oxygen-carrying red blood cells through extravascular and intravascular hemolysis.¹ Persistently low hemoglobin (Hb) can result in frequent transfusions and debilitating symptoms such as severe fatigue, hemoglobinuria, and difficulty breathing (dyspnea).^{2,3}

This letter includes our recommendations for ICER and the underlying rationale.

Recommendation: ICER should clearly distinguish between treatment-naïve and treatment-experienced populations when defining patient populations with PNH. ICER should provide more clarity on its modeling approach and the populations of interest, as clinical studies in PNH vary between treatment-naïve and treatment-experienced patient populations. If ICER's intent is to include both treatment-naïve and treatment-experienced patients in the model, this should be clarified. Given that the treatments included in ICER's draft scope have been studied using different clinical trial populations, merging the two populations for analysis purposes would be difficult, may obfuscate important patient-relevant outcomes, and may not appropriately reflect the treatment intent. Additionally, for treatment-experienced patients, baseline severity and comorbidities (e.g., aplastic anemia) should be explicitly considered in modeling PNH.

Recommendation: Treatment response is best captured by change in Hb and transfusions, which are key elements assessed within the consensus-based criteria published by PNH experts. In the absence of clinical guidelines for PNH, the European Society for Blood and Marrow Transplantation (EBMT) developed categories for classifying hematological response to complement inhibitor treatment.⁴ These categories use well-defined endpoints that are commonly assessed in clinical practice in Europe and the US and encompass a more patient-centered approach to evaluating treatment response. Two of the four treatment response criteria include Hb and transfusions. Using all 4 of these criteria (or at least Hb improvement and transfusion avoidance) in ICER's model would support the use of evidence-based assessment of patient-relevant treatment response. Such categories could be applied across the interventions and comparators of interest.

Further, given these criteria for assessing treatment response have been objectively and independently developed by experts in the PNH field, an assessment of treatment response and the resulting cost per response should be considered by ICER in this assessment. There is published evidence available in the PNH field that provides detailed and reproducible equations for how this analysis was performed (i.e., how a cost per treatment response was calculated).⁵ Evidence of treatment responses assessed by this method have been calculated and published across some complement inhibitor comparators of interest (e.g., eculizumab, pegcetacoplan).⁶⁻¹¹

Recommendation: ICER should use improved Hb as a health state in the base case (rather than stabilized Hb) due to its relevance to patients. ICER's current scope includes

hematological response as a patient-important outcome. However, this broad category includes Hb stabilization and Hb improvement, both of which have been evaluated as endpoints across PNH clinical trials. PNH clinical trial literature defines Hb stabilization as non-worsening of Hb and no measured reduction of Hb greater than 2 g/dL.¹²⁻¹⁵

Conversely, improvement of Hb implies that the treatment helps Hb levels to stay the same or improve to levels close to those of population norms (e.g., ≥ 12 g/dL). Hb improvement is relevant to patients because it has a direct impact on patient fatigue, which is known to be one of the most debilitating symptoms for PNH patients.^{2,3,16} Prioritizing Hb improvement, or the therapeutic aim to do so, would ensure ICER includes an outcome of the highest patient relevance which better tracks patients' quality of life. Hb stabilization can be modeled in a sensitivity analysis.

Recommendation: ICER should clarify the definition of “stable PNH” and consider changing terminology to reflect clinical status and patient quality-of-life. ICER's draft scoping document states that “stable PNH” is likely to be used as a health state in ICER's model, along with breakthrough hemolysis (BTH), spontaneous remission, and death. ICER should reconsider using the term "stable PNH" in favor of terminology that incorporates clinical status and patient quality-of-life into the outcome, as patients can be "stable" with normal hematologic parameters while others are "stable" with poor hematologic parameters and ongoing needs for transfusion. Patients may be considered stable while only achieving suboptimal responses to therapy, which results in poorer clinical outcomes, such as continued transfusion dependence and greater healthcare resource utilization.^{5,17}

Stable PNH could be defined as those patients who reach a major to complete hematological response according to the EBMT consensus criteria, which includes 4 of the most commonly used measures to monitor PNH (e.g., Hb, transfusions, lactate dehydrogenase (LDH), absolute reticulocyte count (ARC)). Several publications also include responses of the various treatments according to this consensus definition.^{12,18}

Importantly, stable PNH should not be defined by BTH alone, which is a more transient marker of disease control, highly variable, and influenced by many complement amplifying conditions. As noted below, BTH should be considered more of a temporary state that is best captured as an adverse event rather than a health state. Of note, BTH is not used as a primary endpoint in recent clinical trials.

Recommendation: Due to variability in definitions for BTH, ICER should use caution when making comparisons across studies and treatments and acknowledge the limitations of those comparisons. The current published literature highlights varying expert definitions of BTH.¹⁸ For example, a real-world analysis of ravulizumab reported rates of BTH following a switch from eculizumab to ravulizumab ranging from 3.1-20.8%, depending on the BTH definition used.¹² The classification of hemolysis also varies in severity, with many cases that are self-limited and do not require transfusions.¹⁸ In addition, there are variations in clinical and subclinical hemolysis. Clinical hemolysis includes patient symptoms, rather than a biomarker alone, and may be more patient-relevant than subclinical hemolysis.

Given that the varying definitions of BTH will impact the rates of BTH reported in clinical trials, we urge ICER to exercise caution when comparing BTH across treatments and making

inferences across studies, and to acknowledge the limitations of those comparisons. ICER's draft scope currently does not account for the heterogeneity in how BTH is defined.

Recommendation: ICER should classify BTH as an adverse event in the model rather than a health state. Investigators who have previously measured BTH as an endpoint in PNH cost-effectiveness models caution that BTH episodes are heterogenous, with the endpoint itself commonly represented by a constellation of symptoms (e.g., fatigue, dyspnea) in tandem with changes in biomarkers (e.g., LDH).²⁰ Hemolysis or changes in LDH in PNH could also manifest due to a variety of reasons, including a lack of treatment effect or a complement-amplifying condition (e.g., pregnancy, surgery, vaccinations). Given the added complexity and uncertainty due to varying BTH definitions, BTH is unsuitable for inclusion as a health state in the model and should instead be included as an adverse event.

Recommendation: ICER should use the most up-to-date data sources and evidence available, including the use of real-world evidence alongside clinical trial data. Given the lack of clinical guidelines and consistent definitions of populations, adverse events, and outcomes for PNH, ICER should use the most up-to-date data sources and evidence, including the use of real-world evidence alongside clinical trial data. It is crucial that ICER review indirect treatment comparisons, real-world efficacy and safety data, and all published PNH models, to capture the current and complete landscape of PNH burden of illness and treatment value.^{21,22,23,24,25}

Recommendation: ICER should elevate the importance of patient-relevant outcomes including increasing Hb and decreasing fatigue. ICER's patient-relevant outcomes should be updated to reflect current goals of treatment in PNH, which have evolved over time. Previously, the primary focus of treatment with C5 inhibitors was avoidance of BTH and mortality. However, with the introduction of newer agents that work on the proximal complement pathway, treatment goals have broadened to include a combination of objectives, including: increasing Hb, reducing transfusion requirements, controlling LDH, decreasing fatigue, improving treatment compliance, and improving other quality-of-life measures. The importance of these goals to patients should be reflected in ICER's analysis.

Apellis appreciates the opportunity to provide comments. If you would like to discuss these comments further, please reach out to me at matthew.cullen@apellis.com.

Sincerely,

Matt Cullen

Matt Cullen

Vice President, US Value, Access, & Policy

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August 14, 2023

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Re: Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria: Background & Scope

Dear ICER PNH Review Team,

Novartis Pharmaceuticals Corporation appreciates the opportunity to provide comments in response to the ICER's Draft Background and Scope Document on Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria (PNH) published on July 25, 2023. Novartis is committed to working in partnership with ICER on this evaluation to help produce a final report that follows methodological best practices.

A hemoglobin/transfusion-based model structure—similar to the ones used in NICE [TA778] (2022) and CADTH Reimbursement Review [SR0748]—best captures treatments' impact on patients with PNH.

In the draft scope, ICER states that the model will likely consist of health states including (i) stable PNH, (ii) breakthrough hemolysis (BTH), (iii) spontaneous remission, and (iv) death.¹ Based on findings from a targeted literature review of existing cost-effectiveness models for PNH treatments, we believe that a hemoglobin (Hb) and transfusion-based model represents best practice in the literature.²⁻⁴ Although cost-effectiveness models for ravulizumab and eculizumab did focus on BTH,⁵⁻⁹ the analytic approach in recent literature has evolved with the introduction of new treatments for PNH. Recent economic models from National Institute for Health and Care Excellence (NICE) [TA778] (2022) model and Canadian Agency for Drugs and Technologies in Health (CADTH) reimbursement recommendation, consist of health states based on transfusion status and Hb levels, which more precisely capture the benefits of the treatments.²

Use of a BTH-based model is problematic for various reasons. First, BTH event frequency in recent clinical trials is relatively uncommon and BTH has not been a primary trial outcome.¹⁰⁻¹⁴ Moreover, measuring treatment efficacy based on BTH is particularly problematic because sample sizes in PNH clinical trials combined with the infrequency of events limit the power to detect treatment efficacy using a BTH outcome.¹⁵ Second, BTH definitions differ across trials, and aligning these results would likely involve making several unrealistic assumptions.^{10-12,16,17} On the other hand, Hb and transfusions are primary or key secondary outcomes reported in the pivotal clinical trials, APPLY-PNH, APPOINT-PNH, ALPHA, PEGASUS, PRINCE, Study 301, and Study 302.^{10-14,16,17} Moreover, these trials are powered for Hb and transfusion outcomes. Third, BTH is transient, and thus unlikely to fully capture unstable disease as a health state.⁹ In addition, the mechanism of BTH may be pharmacokinetic or pharmacodynamic, which is difficult to distinguish without the complete patient profiles.¹⁸ Given the importance of understanding the potential risks for BTH with new treatment options, we recommend ICER incorporate BTH as an event, not as a health state. For these reasons, we believe the current disease landscape is best captured by a model based on Hb and transfusion avoidance.

ICER should consider both complement inhibitor naïve and previously complement inhibitor treated patients.

ICER defines its population of interest as patients with PNH who are eligible for iptacopan or danicopan. We wish to reiterate that pivotal trials for iptacopan include both C5i-naïve and C5i-experienced PNH patients, and thus excluding either group from the study population would be inconsistent with the populations studied with iptacopan. The completed Phase 3 trial for iptacopan (APPOINT-PNH, NCT04558918)¹¹ studies patients who are naïve to C5i therapies. On the other hand, other clinical trials for iptacopan (APPLY-PNH, NCT04820530)¹⁰ and the add-on therapy danicopan (ALPHA, NCT04469465)¹⁹ consider patients with PNH who already received C5i therapies. Furthermore, pivotal clinical trials conducted for the recommended comparator, ravulizumab, include patients who were complement inhibitor-naïve (Study 301, NCT02946463)¹⁷ as well as previously treated (Study 302, NCT03056040).¹⁶ Thus, we recommend a modelling approach with flexibility to account for both patient populations.

Ravulizumab should serve as the primary comparator.

We acknowledge ICER's draft scope includes ravulizumab, eculizumab, and pegcetacoplan as comparators in the economic model, but recommend the use of ravulizumab as the primary comparator. Ravulizumab is the most commonly prescribed treatment for PNH in the US. An internal analysis using real-world data from IQVIA PharMetrics Plus in 2022 showed that the vast majority of patients currently receiving a complement inhibitor treatment for PNH (83.5%) in the US were prescribed ravulizumab (data on file). Data from financial reports confirms that ravulizumab occupies the largest market share (73.7%) among FDA-approved PNH treatments (data on file). In addition, patients and clinicians prefer ravulizumab over eculizumab for treating PNH.^{20,21} ICER's own draft scope states that "ravulizumab is preferred over eculizumab because of the fourfold longer half-life with less breakthrough hemolysis and lower costs."¹ Additionally, direct comparisons between iptacopan, danicopan, and pegcetacoplan are not possible since the clinical trials only use C5 inhibitors (C5i) treatments as the comparators.^{10-12,14,22} Indirect treatment comparisons are possible, but challenging due to differences in outcomes and their definitions across trials.

The societal perspective should be the model base case.

The burden associated with PNH is substantial and may not be accurately captured using a narrow payer perspective. In a survey conducted by the Aplastic Anemia and MDS International Foundation and the National Organization for Rare Disorders (n=163), the most commonly patient-reported reasons for seeking medical attention before diagnosis were fatigue (88%), excessive weakness (73%), and hematuria (62%).²³ Patients' quality of life (QoL) is may be hampered by these debilitating symptoms and comorbidities, particularly ongoing fatigue.²⁴⁻²⁷ While QoL aspects are included in traditional cost effectiveness analyses, physical and mental impairments caused by PNH are associated with considerable disruption to work and lifestyle, leading which can lead to substantial lost productivity costs.²⁸⁻³¹ Given the median age at disease onset is approximately 35 years, accounting for productivity impacts in prime working years is especially pertinent.²⁴ A study using the International PNH Registry (n=506) found that 88 (17.4%) reported PNH as the reason they were either not working or working less.³⁰ A US-based survey of 122 patients with PNH receiving eculizumab or ravulizumab in 2020 included n=53 (43.4%) patients who were gainfully employed. Within this subset, 47.2% of patients reported missing hours at work within the past 7 days due to their disease. Notably, absenteeism (mean: 11.1% [SD: 17%]), presenteeism (31.5% [27%]), work productivity impairment (36.5%

[29%]), and daily activity impairment (39.3% [27%]) due to PNH were reported despite ongoing treatment.²⁶ We highly recommend that ICER use a modified societal impact perspective as the base case of their economic model and take into account productivity impacts of various products used to treat PNH, incorporating inputs such as cost of time spent in travel, administration, and recovery,^{32,33} cost of disease-related absenteeism and unemployment,^{34,35} indirect cost of managing anemia, blood transfusion, thromboembolic events, and renal problems in PNH,^{33,35} productivity impact of treatment setting, dose frequency, and site of administration,³⁶ and impact on caregiver costs and productivity.³⁷

Treatment administration cost and real-world price mark-ups are important cost components to consider in the model.

ICER stated that treatment administration costs will be included in the model. We agree with this decision, and reiterate that these costs would include both health care system costs to administer the treatment (e.g., physician administration cost, additional chair time, home infusion cost), as well as patient time costs, as utilized in various other studies examining PNH treatments.^{3,32,38,39} In addition, we recommend that ICER include the real-world mark-ups on the average sales price (ASP) of intravenously (IV) infused treatments, which if not accounted for, would underestimate the true cost of IV infused treatments and bias the cost-effectiveness estimates. ICER may utilize relevant sources as outlined in the ICER Reference Case to apply an estimate of a provider mark-up for infused products.⁴⁰ An assumption of ASP+6% may be used, consistent with previous ICER evaluations across various therapeutic areas.⁴¹⁻⁴³

We agree with ICER that there are several contextual considerations and other benefits/disadvantages that should be taken into account.

There are numerous contextual considerations ICER should consider in this evaluation. In terms of acuity of need for treatment of individual patients based on short-term risk of death, patients with PNH have a 10-year mortality rate of 29%;⁴⁴ prior to 2007, 5-year mortality rate from PNH diagnosis was 33%.⁴⁵ Approximately 20% of patients with PNH are treated only with supportive care died within 6 years of diagnosis.⁴⁶ The clinical, humanistic, and economic burden of PNH is substantial. PNH is associated with reduced work hours, unemployment, low productivity, and time lost in travel and treatment.^{23-28,47} Caregivers of patients with PNH often experience significant reduction in productivity due to the need to reduce their work hours and days to care for patients with PNH.³⁷ Patients with PNH often experience anemia and require transfusions which negatively impact QoL.⁴⁸ ICER may also account for potential other benefits, such as insurance value for treatment for rare diseases like PNH.⁴⁹

Novartis appreciates the opportunity to provide feedback to ICER for its evaluation of treatments for PNH. We hope these comments will contribute to a more robust assessment.

Sincerely,

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