



Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria

Response to Public Comments on Draft Evidence Report

February 1, 2024

Table of Contents

Manufacturers	2
Alexion Pharmaceuticals, Inc.	2
Novartis	7
Other	13
Partnership to Improve Patient Care (PIPC)	13

#	Comment	Response/Integration
Manufacturers		
Alexion Pharmaceuticals, Inc.		
1.	<p>Alexion believes that the breakthrough hemolysis (BTH) rate used for ravulizumab in the cost-effectiveness model does not reflect ravulizumab’s BTH rate in the population of interest (treatment experienced patients with cs-EVH).</p> <p>ICER assumes that the ravulizumab BTH rate is 17.14% in Table 4.5, p. 23 of the draft evidence report. This figure comes from the C5 inhibitor arm of the APPLY-PNH trial. As described on Table 3.2, p. 8 of the report, only 34.3% of patients in this trial received ravulizumab and the remainder received eculizumab. Therefore, the BTH rate currently used in the model is more representative of eculizumab’s BTH rate, which was the predominant C5 inhibitor used in the APPLY-PNH trial. Given that there is additional data suggesting a much lower BTH rate for ravulizumab (STUDY 301 reported 4% and STUDY 302 reported 0% BTH rate for ravulizumab), we ask ICER to consider all available published evidence and update the current BTH rate assumption for ravulizumab. Moreover, in the ALPHA trial (cs-EVH population) similar observations were made, although there were no pre-defined criteria for BTH and BTH was reported as an adverse event based on investigator discretion.</p>	<p>We thank Alexion for this comment. For the base case, we have revised the ravulizumab BTH rate to be 2.25% based on a weighted average from Study 301 and Study 302. While the study populations from 301 and 302 differ by treatment naive vs experienced, respectively, we do not believe that this would clinically alter the probability of experiencing BTH. We have used a BTH rate of 17.14% in a scenario analysis.</p>
2.	<p>Alexion believes that the comparative clinical effectiveness and long-term cost-effectiveness sections of the draft evidence report are inconsistent with each other. Specifically, the clinical and economic conclusions drawn from comparing iptacopan vs. ravulizumab are discordant.</p> <p>As ICER points out, “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.” Similarly, ICER concludes that “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, the consensus standard of care.” Based on ICER’s definition of its evidence ratings, an</p>	<p>The estimated QALY gain for iptacopan is concordant with the evidence rating of P/I, which ranges from modestly net negative to substantial health benefit. We have now revised the language to include “treatment-experienced with clinically significant EVH” throughout the economic evaluation section.</p>

	<p>“I” would apply to “any situation in which the level of certainty in the evidence is low.” Its “P/I” rating also considers the possibility of a negative health benefit.</p> <p>Given the long-term evidence and significant clinical experience with C5 inhibitors in general, and up to 6 years of data demonstrating the established long-term efficacy and safety of ravulizumab, which is the current standard of care, these ratings seem sensible. However, in contrast with the comparative clinical effectiveness evaluation, the cost-effectiveness section of the report assumes superior efficacy of iptacopan in terms of QALYs gained vs. ravulizumab. Furthermore, many of the model’s clinical inputs for ravulizumab were sourced from the APPLY-PNH trial, where only 34.3% of patients received ravulizumab and the remainder received eculizumab.</p> <p>Additionally, while the comparative clinical effectiveness evaluation appropriately characterizes the trial populations of APPLY-PNH and ALPHA as “Treatment-Experienced with Clinically Significant EVH Population,” the cost-effectiveness analysis consistently omits the fact that these trial populations had clinically significant EVH. Thus, we ask ICER to update the cost-effectiveness evaluation throughout with the appropriate and specific characterization of the trial population and in alignment with the comparative clinical effectiveness evaluation.</p>	
3.	<p>Alexion remains concerned about the use of conventional cost-effectiveness analysis (CEA) for ultra-rare and orphan diseases.</p> <p>Throughout the entire ICER review process of iptacopan and danicopan for PNH, we have expressed our concerns about the potential unintended consequences that the use of CEA may have on patients’ access to innovative medicines, and we would like to reiterate our position. In our previous public comments of the draft scoping document, we cautioned ICER that population-based predictions could be misleading when dealing with highly heterogenous diseases; that patient perspectives are crucial but not taken into consideration in the current framework; real-world evidence is not explicitly included in the comparative effectiveness analysis; and that conventional CEA approaches discourage further investment in innovative medicines for rare and orphan diseases. We strongly believe that while ICER’s intent may be to attempt to quantify the value of new medicines, its current framework, and CEA in particular, can pose additional access barriers to patients living with PNH and</p>	<p>ICER’s mission is to ensure that all patients have access to high-value care at a price they and the system can afford. To achieve this goal, ICER maintains that cost-effectiveness analysis is an essential tool for making decisions about the pricing of every new treatment. We believe we can foster innovation by incentivizing the development of high-value treatments. ICER’s evaluation considers patients’ perspectives and incorporates all available and relevant evidence in the clinical and cost-effectiveness analysis while highlighting any area of uncertainty in these analyses. We have used the best available evidence to inform the inputs in our model and have attempted to be as comprehensive as possible. If you are aware of high-quality evidence we are not using, please provide a specific citation of that evidence, and we will review it for potential inclusion. Further, we provide our findings on the evidence and deliberations on the contextual</p>

	<p>delay the use of new and improved medicines for populations with significant unmet need.</p>	<p>considerations of the condition (e.g., equity, severity, etc.) and other potential benefits of treatment in a public meeting setting that includes patients, clinical experts, and other stakeholders. Finally, we would welcome Alexion to share how the current pricing scheme for eculizumab and ravulizumab and the planned pricing for danicopan reflect the highly heterogeneous nature of PNH.</p>
4.	<p>Page ES1: PNH is caused by uncontrolled activation of the complement pathway of the immune system which causes hemolysis</p> <p>Comment: The life-threatening consequences of PNH are due to uncontrolled terminal complement activation of all blood cell types. It is not just a disease of red blood cell hemolysis but also of terminal complement activation of white blood cells and platelets leading to a prothrombotic state.</p> <p>Recommendation: “PNH is caused by uncontrolled terminal complement activation of red and white blood cells and platelets leading to intravascular hemolysis and a prothrombotic state.”</p> <p>This also applies to the first sentence in p. 1 of the Background section.</p>	<p>We have retained the more original simplified language as our report is written for a lay audience. The proposed mechanism for thrombosis may also be more complex beyond activation of RBC, WBC, and platelets (see Hill et al, Blood, 2013, PMID 23610373).</p>
5.	<p>Page ES1: An FDA-approved intravenous C5 inhibitor (eculizumab infusions every 2 weeks or ravulizumab infusions every 8 weeks) is recommended for the treatment of symptomatic PNH, which comprise up to two-thirds of PNH patients.</p> <p>Comment: The references cited do not support the statement that symptomatic PNH comprises two-thirds of PNH patients. Per FDA labels, ravulizumab and eculizumab are indicated for the treatment of PNH.</p> <p>Recommendation: “An FDA-approved intravenous C5 inhibitor (eculizumab infusions every 2 weeks or ravulizumab infusions every 8 weeks) is recommended for the treatment of symptomatic PNH. which comprise up to two-thirds of PNH patients.”</p> <p>This also needs to be corrected on p. 3.</p>	<p>We have now clarified that the recommendation for treatment of symptomatic PNH is based on clinical experts, and not the FDA: “An FDA-approved intravenous C5 inhibitor (eculizumab infusions every 2 weeks or ravulizumab infusions every 8 weeks) is recommended <u>by clinical experts</u> for the treatment of symptomatic PNH, which comprise up to two-thirds of PNH patients.”</p>
6.	<p>Page ES1: However, even with therapy, about 20% are transfusion-dependent because C5 inhibitors increase extravascular hemolysis (EVH).</p> <p>Comment: C5 inhibitors do not increase EVH but rather Extravascular Hemolysis (EVH) is a mechanistic consequence of</p>	<p>In both the ES and Background sections, we have now clarified that transfusion-dependence is due to the mechanistic consequence of C5 inhibitor therapy.</p>

	<p>treatment with C5 inhibitors and is believed to be caused by ongoing C3 deposition on surviving yet defective red blood cells, which renders them susceptible to phagocytosis in the liver or spleen as they are no longer destroyed by IVH.</p> <p>Recommendation: “However, even with therapy, about 20% are transfusion-dependent because EVH is a mechanistic consequence of treatment with C5 inhibitors and is believed to be caused by ongoing C3 deposition on surviving yet defective red blood cells, which renders them susceptible to phagocytosis in the liver or spleen.”</p>	
7.	<p>Page ES2: Add-on danicopan substantially improved hematologic response versus add-on placebo, including the primary endpoint of change in hemoglobin (+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.</p> <p>Comment: The change in change in hemoglobin for danicopan is incorrect. At 12 weeks, the change in hemoglobin was +2.94 g/dL with a p-value<0.0001.</p> <p>Recommendation: “Add-on danicopan substantially improved hematologic response versus add-on placebo, including the primary endpoint of change in hemoglobin (+2.94 g/dL, p<0.0001), and secondary outcomes of increased hemoglobin ≥ 2 g/dL from baseline without transfusions (60% versus 0%) and less fatigue.”</p> <p>Please apply correction to p. 11 and Table 3.4 on p. 12 as well.</p>	<p>We have reviewed the ALPHA publication, and we are certain that the between group change we reported is correct. We have clarified our language to make it clear that the change in hemoglobin is the change from baseline of add-on danicopan versus the change from baseline of add-on placebo. Table 3.4 does show the change in baseline for each group, as well as the treatment difference between groups.</p>
8.	<p>Page 1: Clone size tends to be either very low or very high, with clinically significant hemolysis typically beginning at sizes greater than 50%</p> <p>Comment: When referring to hemolysis, it is critical to differentiate intravascular, which is life threatening, from extravascular hemolysis, which is not life-threatening.</p> <p>Recommendation: Please be precise throughout the document and refer to IVH when mentioning life threatening consequences and refrain from using the terms hemolysis more generally.</p>	<p>We have now clarified that clone size determines IVH.</p>
9.	<p>Page 6: 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 administered intravenously twice weekly or ravulizumab administered every eight weeks.</p> <p>Comment:</p>	<p>We have now included these details.</p>

	<p>Please add the percent of patients in each C5 inhibitor as detailed on Table 2.3</p> <p>Recommendation: “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; 65.3%) administered intravenously twice weekly or ravulizumab (n=12; 34.3%) administered every eight weeks.”</p>	
10.	<p>Page 9: The ALPHA trial assessed the health-related quality of life as exploratory endpoints.</p> <p>Comment: Please update sentence to note that FACIT-Fatigue score was a key secondary endpoint while other quality of life measures were exploratory.</p> <p>Recommendation: “The ALPHA trial assessed FACIT-Fatigue as a key secondary endpoint and other the health-related quality of life measures as exploratory endpoints.”</p>	We have now revised this statement.
11.	<p>Page 11: Evidence for danicopan’s efficacy in PNH patients who are treatment-experienced on a stable regimen of a C5 inhibitor but still experience clinically significant EVH was derived from the ALPHA, a phase 3, double-blind, randomized trial.</p> <p>Comment: Please add “placebo-controlled” to the sentence.</p> <p>Recommendation: “Evidence for danicopan’s efficacy in PNH patients who are treatment-experienced on a stable regimen of a C5 inhibitor but still experience clinically significant EVH was derived from the ALPHA, a phase 3, double-blind, placebo-controlled, randomized trial.”</p>	We now included this detail.
12.	<p>Page 11: Among 86 participants randomized in the phase 3, double-blinded ALPHA trial, data was available to date for 63 (the first 75% randomized in a planned interim analysis)</p> <p>Comment: The interim analysis of the first 75% randomized patients was pre-specified as the primary analysis set of the study. Under the group sequential design, the positive results based on the interim analysis set of 63 participants would provide primary evidence for efficacy in this phase 3 confirmatory trial, and this interim analysis set would become the primary analysis set.</p> <p>Recommendation: “Among 86 participants randomized in the phase 3, double-blinded ALPHA trial, data was available to date for 63 (approximately 75% of the overall enrolment target in this protocol pre-specified interim efficacy analysis set).”</p>	We have now included this in the report.

13.	<p>Page 11: At the end of 12-weeks, participants treated with danicopan add-on achieved greater least square mean change in LDH from baseline of -23.5 U/L versus -2.9 U/L in the placebo arm, but was not statistically significant.</p> <p>Comment: The statement does not acknowledge that both arms had near normal levels of LDH.</p> <p>Recommendation: “At the end of 12-weeks, participants treated with danicopan add-on achieved greater least square mean change in LDH from baseline of -23.5 U/L versus -2.9 U/L in the placebo arm, but was not statistically significant, and both arms maintained near-normal LDH levels, demonstrating effective control of IVH was maintained with C5 inhibition in both arms.”</p>	We have revised the text to recognize that while the difference was not statistically significant, both groups maintained near-normal LDH levels.
14.	<p>Page 17: The placebo-controlled ALPHA trial demonstrated substantial benefits for danicopan added-on to a C5 inhibitor in reducing blood transfusions and increasing hemoglobin levels and more modest improvement in fatigue.</p> <p>Comment: The observed improvements in fatigue were statistically powered and considered clinically meaningful and thus should not be characterized as modest.</p> <p>Recommendation: “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 and statistically superior more modest improvement in fatigue.”</p>	We have clarified that the improvement in fatigue was clinically meaningful.
Novartis		
1.	<p>ICER should implement a variable cycle length of 1 week for the first 24 weeks, with efficacy beginning immediately.</p> <p>Based on the Draft Evidence Report, the long-term cost effectiveness in ICER’s model utilizes efficacy outcomes for iptacopan based on a 24-week cycle. However, Phase III results from the APPLY-PNH trial demonstrated that mean hemoglobin levels reached nearly 12 g/dL by Week 2 and over the 12 g/dL threshold by Week 4 of treatment with iptacopan, which continued until Week 24, as seen in the Appendix, Figure 1. Therefore, assuming treatment efficacy begins at Week 24 does not accurately represent iptacopan’s onset of action and thus its efficacy is underestimated in the model. We recommend a variable cycle length of 1 week for the first 24 weeks, assuming that treatment efficacy begins at either Week 1 or at Week 2, and every 24 weeks</p>	We thank Novartis for this comment. Our model does not assume treatment efficacy begins at Week 24. Rather, it assumes patients receive treatment efficacy immediately and throughout the first 24 weeks, mirroring what was seen in the APPLY trial.

	thereafter.	
2.	<p>ICER should include ravulizumab’s real-world cost to payers—i.e., with real-world utilization and ASP pricing—in the economic model.</p> <p>Real-world utilization of ravulizumab is associated with higher than expected costs. A real-world data analysis of claims data over 10 years found that the pharmacy costs among 171 patients treated with ravulizumab were \$1,230 per patient per month (PPPM) and increased to \$1,606 PPPM for a subgroup of patients with higher utilization (N=26). Therefore, we recommend that ICER’s estimated ravulizumab cost reflect the costs observed in the real world.</p> <p>Also, the Draft Evidence Report does not clearly state whether the long-term cost effectiveness model applied a markup (6%) to the average sales price (ASP) of the drug price for ravulizumab. An ASP-associated markup is applied to intravenous Medicare Part B covered drugs, and previous ICER reviews have included it in their evaluations. Further, there is real-world evidence for IV infused treatment and medical costs for commercially insured patients in the first year of treatment being 20-60% higher than the drug costs based on their wholesale acquisition price. We recommend that ICER account for the 6% markup and clearly state the inclusion in the Final Evidence Report.</p>	<p>We thank Novartis for this suggestion. The price that we used in the model is based on the CMS allowable price which is inclusive of the 6% markup. We have clarified this in the Evidence Report. Additionally, the per-patient per month cost used in the model from the price for ravulizumab in the model already exceeds the suggested \$1,606 PPPM.</p>
3.	<p>The societal perspective should be the model co-base case rather than a scenario analysis.</p> <p>The narrow payer perspective presented as the base case does not fully reflect the burden associated with PNH. The physical and mental impairments caused by PNH that lead to productivity loss for patients with PNH are important and should be highlighted by presenting the societal perspective as a co-base case. Physical and mental impairments caused by PNH are associated with considerable disruption to work and lifestyle, which may lead to substantial lost productivity costs. Given the median age at disease onset is around 35 years, accounting for productivity impacts in prime working years is especially pertinent. A study of 506 patients aged 18-59 years enrolled in the International PNH Registry as of June 2016 found that 88 (17.4%) patients reported PNH as the reason they were either not working or working less. A US-based survey of 122 patients with PNH receiving eculizumab or ravulizumab in 2020 included 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. Notably, absenteeism (mean: 11.1% [SD:</p>	<p>We agree that productivity loss is important to include in a societal perspective analysis. As such, we have included productivity losses that were estimated by Levy et al. (2019) which Novartis referenced (8). This study included travel time, wait time, infusion time, and recovery time to estimate costs associated with productivity loss for those receiving ravulizumab. Novartis also mentions how varying proportions of patients have productivity impacts due to receiving ravulizumab. In the modified societal perspective analysis, our model assumes 100% of patients experience impacts on productivity. Finally, Novartis mentions a recent cost-effectiveness analysis that projected 730 hours saved for iptacopan vs. ravulizumab using a lifetime horizon. Using the 330 minutes of treatment duration associated with receiving ravulizumab from Levy et al (2019), our model exceeds the aforementioned</p>

	<p>17%]), presenteeism (31.5% [27%]), work productivity impairment (36.5% [29%]), and daily activity impairment (39.3% [27%]) were reported among patients with PNH despite ongoing treatment. There is also evidence that mode of administration, which ICER notes in its Draft Evidence Report as being important to patients, can impact productivity. Additionally, results from a cost-effectiveness analysis presented at the American Society of Hematology (ASH) 2023 conference indicated that iptacopan oral therapy was projected to save patients and nurses approximately 730 and 2,920 hours, respectively, over a lifetime compared to intravenous (IV) ravulizumab in PNH-specific care averted.</p> <p>While ICER does consider the modified societal perspective as a scenario analysis, we recommend that ICER present the societal impact perspective as a co-base case and explicitly take into account productivity impacts of PNH on patients as well as their caregivers.</p>	<p>projection by estimating 803 hours over a lifetime horizon. However, our base case uses a 5-year time horizon for reasons specified in the evidence report.</p>
<p>4.</p>	<p>The evidence ICER used to model excess mortality due to major adverse vascular events (MAVEs) is inappropriate for the model population and does not fully reflect the evidence available.</p> <p>We acknowledge ICER’s concerns regarding the impact of MAVEs in PNH treatments. However, it is crucial to note that the source for excess mortality associated with MAVE occurrence cited in the economic model is based on a retrospective analysis of patients who had <u>not</u> received eculizumab, which is not in line with the treatment experienced inclusion criteria in the model. Furthermore, long-term studies of eculizumab have found that survival among treated patients was significantly better than similar patients managed before eculizumab (P < 0.001). One study among 4,118 patients with PNH with ≥14 years of follow-up data found 49% higher survival among patients during eculizumab-treated time compared to untreated time. Additionally, the one iptacopan-treated patient in the APPLY-PNH trial that experienced a MAVE continued to receive iptacopan as the event was considered unrelated to the therapy. Therefore, we recommend ICER follow the methodology used in other published cost- effectiveness models which apply a general population level mortality, with no excess mortality associated with MAVE among patients with PNH.</p> <p>Finally, in the Draft Evidence Report, ICER stated the value of disutility used for MAVE to be - 0.00064, which was assumed to last one model cycle (24 weeks). However, the duration of treatment of a MAVE varies by the type of event and can be resolved in as short as 3</p>	<p>In the scoping phase with clinical experts, we were informed that MAVE was the primary driver of mortality in patients with PNH. We have included a scenario analysis where we zeroed out the excess mortality associated with MAVE.</p>

	<p>weeks.</p> <p>Therefore, ICER’s model overestimates disutility from MAVE, and we recommend ICER account for MAVE duration more accurately in its economic model.</p>	
5.	<p>We agree with ICER that there are several contextual considerations and other benefits/disadvantages that should be taken into account.</p> <p>Benefit of oral therapies and patients’ ability to manage and sustain treatment given the complexity of regimen.</p> <p>Oral therapies provide a means of overcoming accessibility barriers for patients living in more remote rural areas which require greater travel. C5 inhibitors are administered intravenously every 2 or 8 weeks depending on the type. A study estimated that treating 100 patients with PNH with eculizumab for 2 years in a clinic would necessitate 25,920 hours of travel, administration, and recovery, generating \$518,400 in lost productivity. The corresponding estimate for ravulizumab was \$184,800, given its reduced dosing frequency. A second study estimated that a US patient with PNH would spend 249 hours in treatment with eculizumab over 2 years, which decreased by 77% with IV ravulizumab and by 89% with subcutaneous ravulizumab. Furthermore, a cost-effectiveness analysis found that iptacopan oral therapy is projected to save patients and nurses approximately 730 and 2,920 hours, respectively, over a lifetime compared to IV ravulizumab in PNH-specific care averted.</p>	<p>We agree that oral therapies will save time and have included productivity losses in the societal perspective model that were estimated by Levy et al. (2019) that Novartis referenced (8). This study included travel time, wait time, infusion time, and recovery time to estimate costs associated with productivity loss for those receiving ravulizumab.</p>
6.	<p>Patients’ and caregivers’ ability to achieve major life goals, related to education, work, or family life.</p> <p>The economic burden associated with PNH is substantial, with key drivers including hospitalizations, transfusions, and lost productivity. An analysis of data from the International PNH Registry—which included 377 patients who had a PNH diagnosis regardless of clone size, other bone marrow disorders (BMD), symptoms, or treatments—found that among 109 patients who worked at a paid job, 30% had missed work in the preceding 6 months due to PNH. In another analysis of 229 patients enrolled in the International PNH Registry who started eculizumab treatment before August 1, 2016, emergency room visits (incidence rate ratio [IRR]: 0.33 [95% confidence interval (CI): 0.20-0.54]) and number of missed workdays due to PNH symptoms</p>	<p>We have included ravulizumab-specific productivity loss as mentioned above. Furthermore, other productivity loss not included is anticipated to affect the PNH population similarly regardless of treatment choice, so this would not lead to incremental differences in our model.</p>

	(IRR: 0.48 [95% CI: 0.25-0.93]) decreased after eculizumab initiation.	
7.	<p>ICER should consider additional cost-offsets due to iptacopan in the shared savings scenario analysis.</p> <p>The shared savings scenario analysis undertaken by ICER does not consider the societal perspective and other value elements such as insurance value for treatment for rare diseases like PNH. Importantly, in this scenario, the comparator is de facto no treatment rather than the standard of care, which is against economics best practices. To make this analysis more robust, ICER should take into consideration other cost-offsets from productivity and treatment adherence from a less complex regimen, which are reflected in the societal perspective scenario analysis of the model.</p>	The cost-offset cap scenario is intended to acknowledge situations where a substantial percentage of the traditional value-based price comes from cost offsets of a comparator therapy. This scenario considers health system cost-offsets only, and a separate scenario analysis is included to consider the societal perspective without the application of a cap on cost-offsets. To clarify further, the cost-offset cap scenario analysis retains standard of care (C5 inhibitor) as the comparator, however, caps the annual cost-offsets assigned to the new therapy to \$150,000 per year.
8.	<p>Although ICER's economic model does not include treatment-naïve patients, iptacopan is approved by the US Food and Drug Administration (FDA) for adults with PNH.</p> <p>Iptacopan is approved by the FDA for adults with PNH. Iptacopan was studied in both complement inhibitor-experienced adults with PNH and complement inhibitor-naïve adults with PNH. The FDA label for iptacopan provides efficacy results from APPOINT-PNH, stating 77.5% treatment-naïve patients (31/40) achieving a sustained increase (between Day 126 and Day 168) in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions based on central laboratory hemoglobin values. In a sensitivity analysis, 87.5% (95% CI: 73.2%, 95.8%) of patients (35/40) achieved a sustained increase (between Day 126 and Day 168) in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions, including local laboratory hemoglobin values when central laboratory hemoglobin values were not available. We note ICER's concern on the single-arm nature of the APPOINT-PNH trial. We reiterate that it was designed as a single-arm trial as a placebo-controlled design was considered unethical in countries where anti-C5 therapies were available considering the evidence of iptacopan's benefit in interim analyses of the Phase II X2201 and X2204 studies. Additionally, this supported the registration of iptacopan as a treatment for countries where, at the time of study initiation, anti-C5 therapies were not available (e.g., China), thus an active comparator design was not possible.</p>	We had asked Novartis for data multiple times in order to consider doing an analysis in the treatment naïve population. In the absence of data, we are unable to perform the suggested analysis.
9.	The use of 21% as the percentage of patients not controlled on current therapy in the budget impact model is inappropriate if applied to the entire prevalent population.	To clarify, our estimate of the eligible patient population was based on 1) The prevalence of PNH (12.5 cases per 1,000,000 individuals), 2) The percentage of patients

	<p>The budget impact analysis uses the estimate from Kulasekararaj et al. (21%) as the filter for percentage of patients that are treated with eculizumab, which would translate to those experiencing a clinically significant extravascular hemolysis and would be eligible to switch to iptacopan or danicopan as an add-on therapy. However, the budget impact model structure does not mention a filter for the proportion of patients receiving any treatment for PNH, so this proportion may be inappropriate if applied to the entire prevalent population. Based on a real-world analysis of treatment patterns among newly diagnosed patients with PNH, 26.4% are treated with any PNH-indicated medication. We suggest that ICER use this estimate of the percentage of C5 inhibitor-naïve patients being treated as a preliminary filter, and then apply the percentage not controlled to this subgroup of treated patients with PNH.</p>	<p>with PNH who are symptomatic and eligible for a C5i (61.3%), and 3) The percentage of patients that are not controlled on current therapy (21.3%). The use of 21.3% was not applied to the entire prevalent population. It was applied to the subset of patients who were assumed to be symptomatic and eligible for therapy. This subset of patients is meant to represent the percentage of patients who are potentially eligible to receive therapy and is based on registry data representing the percentage of patients that are considered symptomatic based on the need for red blood cell transfusions.¹ Our estimate of 61.3% also aligns with input from clinical experts who indicated that approximately two-thirds of patients are likely to be uncontrolled on C5is. While we appreciate Novartis providing a source to represent the percentage of patients who are treated with PNH-indicated medication, we would like to emphasize that 26.4% is based on a retrospective claims analysis and is likely an underestimate of the patients who may be eligible for therapy.</p>
--	---	---

#	Comment	Response/Integration
Other		
Partnership to Improve Patient Care (PIPC)		
1.	<p>ICER’s choice of model underestimates the complexity of PNH and ignores major aspects of disease burden.</p> <p>As PIPC has pointed out in the past, ICER tends to oversimplify models, which can frequently lead to assessments that do not account for the true burden of disease. ICER’s PNH model is a simple three-state model that relies heavily on whether the PNH patient has reached a specific level of released hemoglobin, and subsequently whether that patient becomes transfusion dependent. This is an oversimplification of a complex condition.</p> <p>Chronic anemia, fatigue, and the need for transfusion are common outcomes for patients with PNH. Yet, chronic anemia and fatigue are not incorporated into the ICER model. Including them would present a more holistic picture of the patient experience and improvement with treatment. Transfusion is included, but without significant regard for variance between the treatment arms, so the model is not able to present an accurate picture of the disease and potential treatment effects. The longer-term impacts of transfusion dependence and iron overload are also ignored by the model, which is a source of considerable burden to PNH patients. Transfusion dependence has a negative effect on a patient’s quality of life and also requires substantial resources, including hospital admissions. Spending some time to more thoroughly include these factors in the model would have presented both a more representative picture of patient improvement and potential cost savings related to treatment.</p>	<p>We thank PIPC for their comment. As mentioned in the report, this model structure has been used in previous economic evaluations and was the only viable model structure given data availability and the manufacturers’ unwillingness to provide additional data to perform a more detailed analysis. We agree that chronic anemia, fatigue, and need for transfusion are common outcomes in PNH. These components are included in the utilities for transfusion dependence as the utility values are directly informed by patients in need of transfusion who are experiencing the symptoms mentioned.</p>
2.	<p>ICER should rely more heavily on real world evidence. ICER has derived utility data from RCT data but could have chosen to run scenarios using utilities from real world studies or PNH cohorts. There are numerous reasons for preferring real-world cohort-based estimates of utilities, as clinical trials are renowned for recruiting “healthier” patients than those people who make up the real-world population of need. It is also well known that trials tend to include a placebo effect on patients in the comparator arm. In addition, patients in RCTs tend to receive far more non-treatment specific care and attention; symptom management interaction with clinicians</p>	<p>ICER uses the best available evidence to inform the inputs in the model. If you are aware of any high-quality, real-world evidence that we could have used, please provide a specific citation, and we will review it for potential inclusion. Furthermore, we conducted sensitivity analyses to assess the impact of any parameter uncertainty for the key model inputs, including the utility. The findings of the sensitivity analyses are presented in the report.</p>

	<p>and other medical staff, than the average patient in a real world setting. As such quality of life measures in patients' non-response states are often higher for patient in RCTs than in real world cohort studies. Given this reality, relying on RCT data for utilities does not provide an accurate picture of the quality of life of the holistic patient population. To gain a more comprehensive understanding of improvement with treatment, ICER would do better to rely on real world evidence as the basis for its models.</p>	
<p>3.</p>	<p>ICER should make more of an effort to address patient heterogeneity.</p> <p>PNH is a clinically heterogeneous disease. For example, for some patients, disease progression is characterized by florid intravascular, complement-mediated hemolysis, whereas in others, bone marrow failure dominates the clinical picture with modest or even no evidence of hemolysis observed.</p> <p>If the purpose of ICER is to provide insight into decision-making around the value of any new therapy for patients, it needs to produce an estimate – or a range of estimates – for as many of that wide range of patients, or patient types, as is possible. ICER's current model does not do this. Instead, ICER defers to the "average patient." This does not provide useful information on value that reflects a diverse population. It is well established that generating and reporting of differential value assessment estimates across subgroups leads to substantial health gains, both through treatment selection and coverage. If ICER seeks to develop reports that provide actionable and reliable information to health policy decision makers about the value of new therapies, it needs to move away from the assumption that all patients are average – an important step toward health equity.</p>	<p>ICER does not think patients are average. ICER thinks drugs sold in the US have an average price. ICER evaluates drugs, not people.</p>
<p>4.</p>	<p>ICER's model does not account for the true cost of PNH. As PIPC has commented to ICER in the past, ICER's assessments would be more credible and more accurately depict value if they incorporated full societal costs and not just costs to the health care system. That being said, this model omits even some obvious costs to the health care system. Specifically, the model appears to capture only treatment cost and transfusion cost data. This does not paint a full picture, as patients with PNH will have many interactions with the healthcare system, in both inpatient and outpatient clinical settings, alongside the transfusion costs.</p> <p>The paper that the ICER model references for its unit cost for transfusions clearly states that the cost of transfusions is just a tiny fraction of overall healthcare costs associated with PNH. In this study it was estimated that a transfusion-dependent PNH patient's transfusion costs make up just \$30,000 of an</p>	<p>We do incorporate societal costs in the modified societal perspective. With regards to the paper by Cheng et al (2021) that assessed total annual healthcare cost differences between the transfusion-dependent and transfusion-free patients, there are issues that limit its applicability for use in our analysis. Among them, this study assessed eculizumab patients, and therefore, it is possible that they received an up-dose of treatment during their transfusion-dependency that could have contributed substantially to the difference in direct medical costs. Additionally, as noted on Figure 4a, footnote 2, the costs were only adjusted for gender and aplastic anemia. However, Table 1 shows that the</p>

<p>annual mean of \$409,000 per year, the bulk of which are made up from outpatient visits and inpatient costs of \$190,000 and \$170,000 respectively. The paper suggests that a transfusion-dependent PNH patient may have total annual healthcare costs in the region of \$409,000 as compared to a transfusion-free PNH patient of around \$190,000. As both Iptacopan and Danicopan show rates of transition to transfusion dependent state at just a fraction (5-27%) of that in the ravulizumab arm (0.036 compared to 0.739 – 5%; 0.167 compared to 0.619; 27%), this would be a meaningful input.</p> <p>Despite this data, ICER’s model does not capture the savings of patients being on a drug that reduces the annual rate of a patient moving from a state that costs \$200,000 per year to a state that costs \$400,000 per year. Instead, it shows each patient having comparable annual “non-drug” costs over five years and that total “non-drug” cost is a maximum of \$104,000 over five years. These numbers do not reflect the research ICER cites. PIPC urges ICER to take a closer look at its inputs and ensure it is capturing the full value of the treatments in question.</p>	<p>two groups were significantly different at baseline (3 months before the study follow up/observational period) for all-cause and PNH-related healthcare resource utilization and healthcare costs. Thus, the transfusion dependent group, for unspecified reasons, were already a higher cost group at baseline. If these baseline variables were adjusted for, the large difference seen in direct medical costs between the two groups would be reduced.</p>
--	---