RESEARCH ARTICLE OPEN ACCESS

Effectiveness of Iptacopan Versus C5 Inhibitors in Complement Inhibitor-Naive Patients With Paroxysmal Nocturnal Haemoglobinuria

Matthew Holt[1] | Richard J. Kelly[1] | Jilles M. Fermont[2] | Soudeh Ansari[3] | Marion Dahlke[2] | Isabelle Brindel[4] | Lynda Maafa[4] | Flore Sicre de Fontbrune[4,5] | Régis Peffault de Latour[4,5]

[1]St. James's University Hospital, Leeds, UK | [2]Novartis Pharma AG, Basel, Switzerland | [3]Novartis Institutes for Biomedical Research, Cambridge, Massachusetts, USA | [4]French Référence Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Paris, France | [5]Assistance Publique Hôpitaux de Paris, Université Paris Cité, Paris, France

Correspondence: Matthew Holt (matthew.holt@nhs.net)

Received: 15 April 2025 | **Accepted:** 21 April 2025

Funding: This study was funded and conducted by Novartis as part of a research collaboration. Financial support for medical editorial assistance was provided by Novartis Pharma AG, Basel, Switzerland.

Keywords: APPEX | APPOINT-PNH | C5 inhibitors | iptacopan | paroxysmal nocturnal haemoglobinuria

ABSTRACT

Background: Paroxysmal nocturnal haemoglobinuria (PNH) is characterised by haemolytic anaemia, bone marrow failure and thrombosis. The single-arm phase 3 APPOINT-PNH trial (NCT04820530) investigating iptacopan monotherapy in complement inhibitor-naive patients demonstrated significant haemoglobin concentration improvements.

Methods: We used target trial emulation to retrospectively predict outcomes if APPOINT-PNH trial patients had received C5 inhibitors instead of iptacopan. Estimates were derived from the real-world APPEX cohort treated with routine C5 inhibitors. The study used benchmarking and comparative effectiveness to evaluate the haematological response in APPOINT-PNH if patients had received C5 inhibitors. Treatment effect was estimated using propensity scores to model the probability of trial inclusion based on baseline covariates, followed by fitting an outcome model to the APPEX cohort.

Results: The analysis of 125 patients showed all estimated treatment effects (95% confidence interval) favoured iptacopan over C5 inhibitors: differences in the proportion of patients achieving haemoglobin increase from baseline of ≥ 2 g/dL, 68.2% (40.9–95.6); haemoglobin levels of ≥ 12 g/dL, 53.4% (31.4–75.3); transfusion independence, 38.8% (15.1–62.5); ratio of percent change from baseline in lactate dehydrogenase levels, 0.51 (0.40–0.67); change from baseline in reticulocytes, -75.5×10^9/L (−106.9, −44.2).

Conclusions: Results indicate C5 inhibitor-naive patients with PNH may experience greater haematological response with iptacopan than with C5 inhibitors.

Trial Registration: ClinicalTrials.gov identifier: NCT05842486

1 | Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare condition characterised by haemolytic anaemia, bone marrow failure and thrombosis [1–3]. The incidence of PNH is estimated at 0.1–0.35 per 100,000 individuals and the 15-year prevalence is reported as 1.6–3.8 per 100,000 individuals [4–6]. PNH is caused by acquired somatic mutations in haematopoietic stem cells

leading to the production of red blood cells (RBCs) deficient in glycosylphosphatidylinositol-anchored proteins and subsequent causing vulnerability to complement-mediated intravascular haemolysis [7].

Approved treatments for PNH include C5 inhibitors such as eculizumab and ravulizumab that target the underlying intravascular haemolysis [7–9]. However, extravascular haemolysis occurs as a pharmacological consequence of C5 inhibition that leads to anaemia in a significant proportion of patients (50%–82%) and transfusion dependence in some patients (8%–32%) [10–12].

Iptacopan, a first-in-class, oral factor B inhibitor, is a novel treatment for PNH that can inhibit intravascular haemolysis and prevent extravascular haemolysis, thereby prolonging RBC survival [13]. The single-arm, multicentre, open-label, phase 3 APPOINT-PNH trial (NCT04820530), which investigated iptacopan monotherapy in complement inhibitor-naive adult patients, demonstrated clinically significant improvements in haemoglobin levels in the absence of RBC transfusions (RBCTs) [13]. APPLY-PNH was a randomised, multicentre, open-label, phase 3 trial (NCT04558918) that enrolled patients with PNH and persistent anaemia despite being on a stable regimen of C5 inhibitors [13]. In the APPLY-PNH trial, switching to iptacopan monotherapy showed superior efficacy over continued treatment with C5 inhibitors [13]. However, data comparing the haematological response to iptacopan with that to C5 inhibitors in complement inhibitor-naive patients with PNH are not available.

Given that APPOINT-PNH was a single-arm trial and that a randomised head-to-head trial of iptacopan versus C5 inhibitors in complement inhibitor-naive patients has not been conducted to date, target trial emulation and causal inference methods can be used to leverage observational data on C5 inhibitors to fill the knowledge gap [14–19]. This approach, known as target trial emulation, enables the analysis of observational data in a manner that attempts to emulate a randomised trial (referred to as a 'target trial') [14, 15, 20–22]. The present study aimed to estimate the treatment outcomes that would have been observed if patients from the APPOINT-PNH trial had received C5 inhibitors instead of iptacopan, using data from routine clinical practice.

2 | Methods

2.1 | Study Design

The retrospective noninterventional APPEX study (NCT05842486) was used for benchmarking and estimating the comparative effectiveness of iptacopan versus C5 inhibitors in complement inhibitor-naive adult patients with PNH. Evaluation of effectiveness was based on the use of a target trial framework to emulate a two-arm study of iptacopan versus C5 inhibitors (Table S1) [17, 20]. The study was reviewed and approved by the hospital data access committee in Leeds. Secondary use of data from the RIME registry (NCT04781790) in France was approved by the Ethics Committee Ile de France IV. The study was conducted in accordance with the Declaration of Helsinki. All patients provided permission for their medical data to be used for research purposes. Further details are available in the Supporting Information.

2.2 | Setting

Data were extracted from hospital databases in France (Hôpital Saint-Louis, Paris) and the United Kingdom (St. James's University Hospital, Leeds; Figure S1), with sample collection performed between 1 January 2007 and 31 December 2022 (Supporting Information). The extracted laboratory data were collected during routine outpatient visits.

2.3 | Patients

The same eligibility criteria as those for the APPOINT-PNH trial [13] were applied to the APPEX cohort (Supporting Information).

2.4 | Endpoints

Effectiveness of the haematological response was defined according to the following endpoints:

1. Proportion of patients initiating treatment with C5 inhibitors who would have achieved an increase from baseline in haemoglobin levels of ≥ 2 g/dL (between Days 100 and 200) in the absence of RBCTs (occurring between Days 15 and 200)
2. Proportion of patients initiating treatment with C5 inhibitors who would have achieved a sustained haemoglobin level of ≥ 12 g/dL (between Days 100 and 200) in the absence of RBCTs (between Days 15 and 200)
3. Proportion of patients initiating treatment with C5 inhibitors who would have achieved transfusion avoidance (between Days 15 and 200)
4. Percentage change from baseline in lactate dehydrogenase (LDH) levels (between Days 15 and 200)
5. Change from baseline in absolute reticulocyte count (between Days 1 and 200).

Additional analyses included the rate of breakthrough haemolysis during the initial 24-week treatment period starting from the index date to up to Day 200 and mean haemoglobin levels over time (sustained effect). See Supporting Information for details.

2.5 | Statistical Analysis

Potential confounders and prognostic factors that were available in the APPEX dataset and known to affect haematological response were identified through a systematic literature review and expert assessment. Missing data in the APPOINT-PNH trial were modelled using multiple imputation [13]. In the APPEX cohort, patients were followed up according to standard of care rather than in the same schedule of assessment as that for the APPOINT-PNH trial. Annualised rates in the APPEX cohort within the first 200 days after the index date were obtained from a negative binomial model. A detailed description of the confounder assessment and statistical analysis, including propensity score and sample size calculation and benchmarking, comparative effectiveness and sensitivity analysis is available in the Supporting Information.

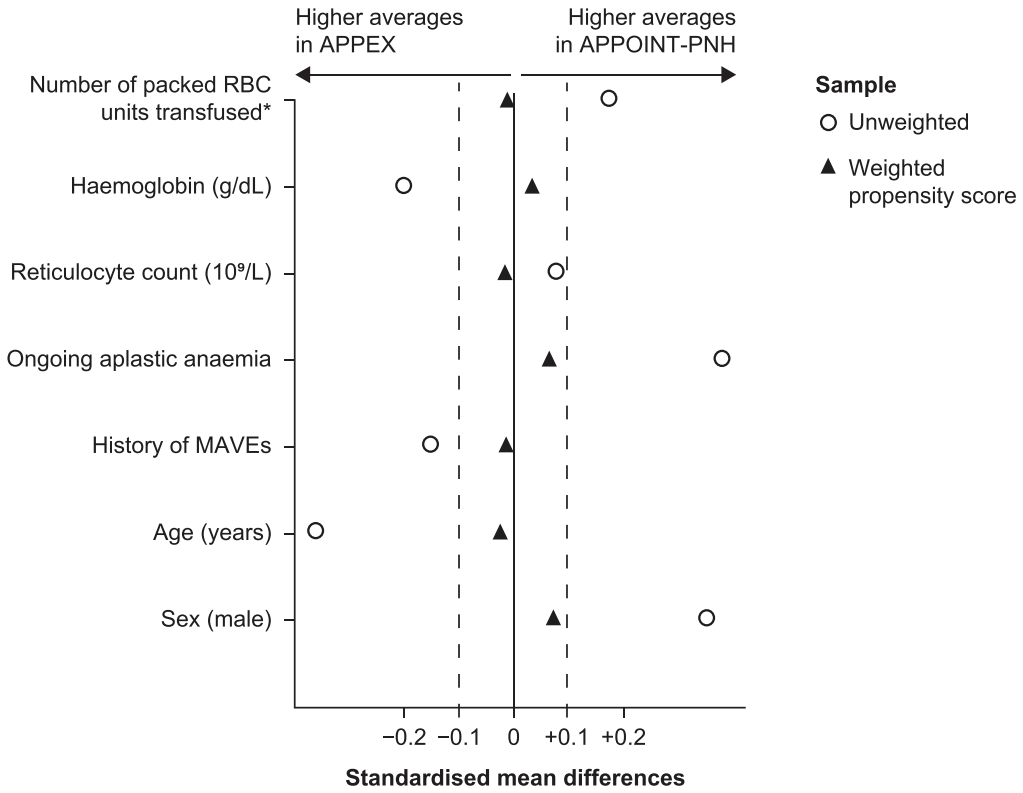

FIGURE 1 | Love plot showing the balance in baseline covariates between the APPOINT-PNH cohort and the APPEX cohort before and after weighting. The circles and triangles represent the unadjusted and adjusted variables used in the propensity score, respectively, and indicate differences between the retrospective cohort of patients and patients in the APPOINT-PNH trial. The standardised mean differences for all variables were < 0.10, indicating a good balance in the two patient populations after adjustment.

*Total number of units transfused in the prior 6 months.

MAVE, major adverse vascular event; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell.

3 | Results

3.1 | Study Population

In total, 92 patients were enrolled in the APPEX study. The analysis sample included 85 patients after excluding five patients who lacked data on baseline reticulocyte measurements, one patient who failed screening and one patient who had no documented data on the occurrence of transfusions (Figure S2). Overall, 125 patients were analysed in the retrospective study, which included 40 patients in the APPOINT-PNH cohort and 85 patients in the APPEX cohort (France, $n = 47$; United Kingdom, $n = 38$). The distribution of baseline characteristics before and after applying propensity score weights obtained from the propensity score model is shown in Figure 1 and Table S2. After weighting, baseline covariates between the APPOINT-PNH and APPEX cohorts were well balanced, with all standardised mean differences falling within ±0.10.

3.2 | Benchmarking

The estimated treatment effectiveness in terms of haematological response was greater with iptacopan than with C5 inhibitors for all five endpoints investigated (Figure 2A–E). The unweighted estimates were similar to the weighted estimates.

3.3 | Comparative Effectiveness

Differences in the proportion of patients achieving a haemoglobin level increase of ≥ 2 g/dL, haemoglobin levels of ≥ 12 g/dL and transfusion independence were all in favour of iptacopan compared with C5 inhibitors (Table 1). Both the ratio of percentage change from baseline in LDH levels and the difference in change from baseline in reticulocyte count were also in favour of iptacopan (Table 1).

3.4 | Mean Haemoglobin Levels Over Time

Mean haemoglobin levels increased over time for patients in both the APPEX cohort and the APPOINT-PNH cohort (Figure 3). At Week 24, the mean (standard deviation) haemoglobin level was 9.82 g/dL (1.74) in patients treated with C5 inhibitors versus 12.6 g/dL (standard error, 0.2) [13] in patients treated with iptacopan in the APPOINT-PNH trial.

3.5 | Breakthrough Haemolysis

Annualised rates of breakthrough haemolysis events in the APPEX study were based on observed numbers up to Day 200. In total, 15 events were observed for 10 patients (11.8%) within

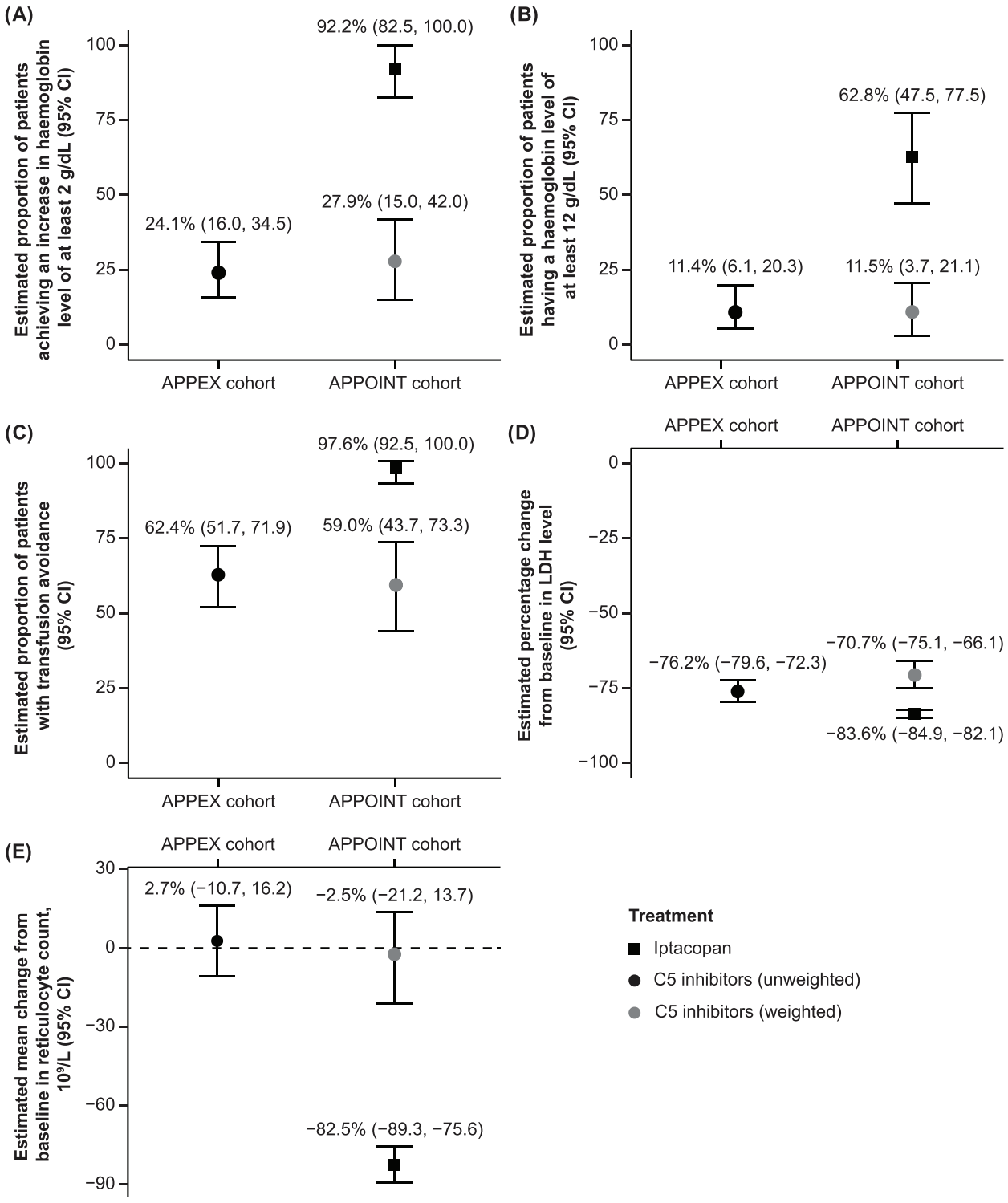

FIGURE 2 | Treatment outcomes for effectiveness with C5 inhibitors in the APPEX study and APPOINT-PNH trial cohorts (overall analytical cohort [$n = 125$]). (A) Haemoglobin level increase of ≥ 2 g/dL from baseline in the absence of RBCTs, (B) Haemoglobin level of ≥ 12 g/dL in the absence of RBCTs, (C) transfusion avoidance, (D) percentage change from baseline in LDH levels, (E) change from baseline in reticulocyte count.
CI, confidence interval; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; RBCT, red blood cell transfusion.

this timeframe. Of the 10 patients experiencing breakthrough haemolysis events, eight received transfusions in conjunction with the detection of the event. Therefore, the estimated annualised rates in the APPEX cohort were 0.30 (95% confidence interval [CI]: 0.16–0.65) events/year within the first 200 days after the index date. The corresponding rates based on observations up to 52 weeks were 0.30 (95% CI: 0.16–0.50) events/year. No breakthrough haemolysis events were observed during the 24-week core treatment period for patients in the APPOINT-PNH trial [13].

TABLE 1 | Comparative effectiveness osf iptacopan and C5 inhibitor treatment for haematological endpoints in APPEX and APPOINT-PNH.

Endpoint	APPEX n/M	APPOINT-PNH n/M	Estimated difference based on a comparative effectiveness model comparing iptacopan to C5 inhibitor % (95% CI)
Proportion of patients with an increase from baseline in haemoglobin level of ≥ 2 g/dL[a] in the absence of RBCTs[b]	19/79	31/33	68.2 (40.9–95.6)[c]
Proportion of patients having haemoglobin levels ≥ 12 g/dL[a] in the absence of RBCTs[b]	9/79	19/33	53.4 (31.4–75.3)[c]
Proportion of patients with transfusion avoidance[b]	53/85	40/40	38.8 (15.1–62.5)[c]
Percent change from baseline in lactate dehydrogenase levels (ratio)[b]	NA	NA	0.51 (0.40–0.67)[c]
Change from baseline in reticulocyte count (difference in change from baseline, $\times 10^9$/L)[d]	NA	NA	−75.5 (−106.9, −44.2)[c]

Abbreviations: CI, confidence interval; M, number of evaluable patients; n, number of responders; NA, not applicable; PNH, paroxysmal nocturnal haemoglobinuria; RBCT, red blood cell transfusion.

[a]Endpoint for C5 inhibitor treatment included measurements between Days 100 and 200 (mean of all available measurements), which was equivalent to Weeks 18–24 in APPOINT-PNH.

[b]Endpoint for C5 inhibitor included measurements between Days 15 and 200, which was equivalent to Weeks 2–24 in APPOINT-PNH. Transfusion avoidance was assessed between Days 14 and 168 in APPOINT-PNH.

[c]Derived using the orthogonalized score form of the efficient influence function and cross-fitting.

[d]Endpoint for the C5 inhibitor included measurements between Days 1 and 200.

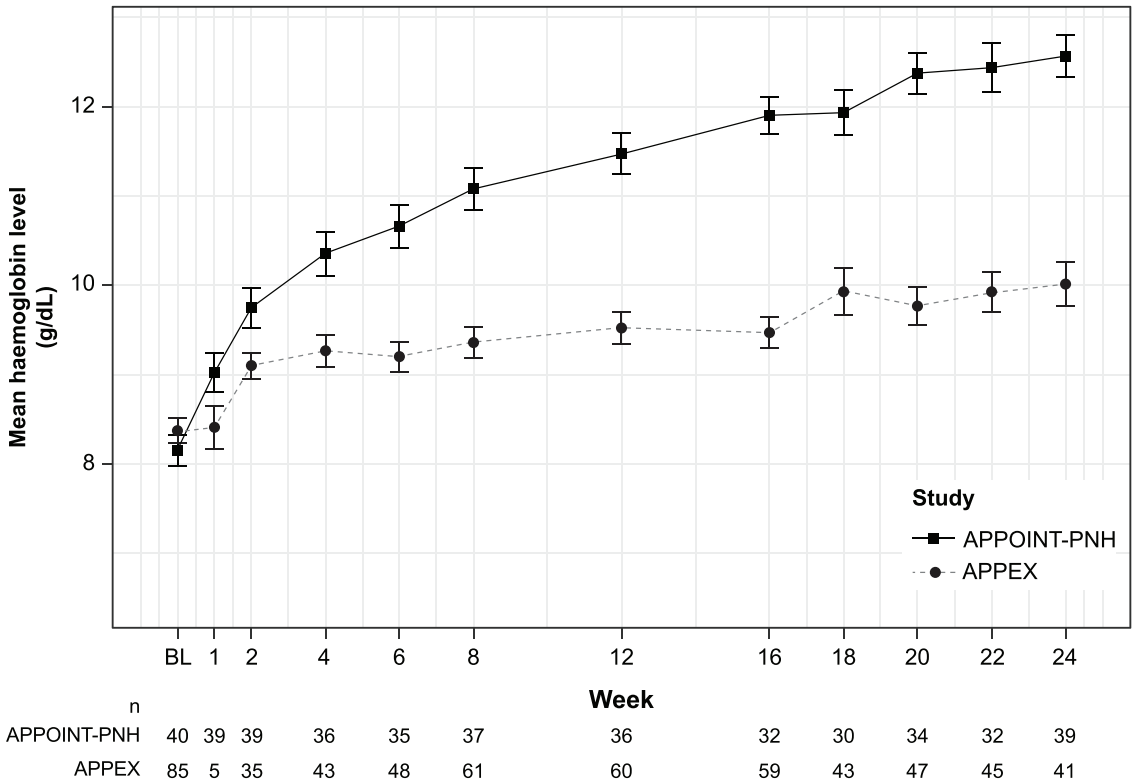

FIGURE 3 | Mean haemoglobin levels over time in the APPOINT-PNH cohort versus the APPEX cohort. Data are shown as the mean ± SE values of the haemoglobin level at each visiting time.

BL, baseline; n, number of patients with available data; PNH, paroxysmal nocturnal haemoglobinuria; SE, standard error.

3.6 | Sensitivity Analyses

Using the alternative assessment windows, the predicted proportions were similar to those reported in the primary analysis for achieving a haemoglobin level increase of ≥ 2 g/dL from baseline in the absence of RBCTs (Table S3). However, for achieving a fixed haemoglobin level of ≥ 12 g/dL in the absence of RBCTs, the observed proportions were lower in both windows than in the primary analysis.

4 | Discussion

This is the first study to have compared treatment outcomes in complement inhibitor-naive patients treated with iptacopan versus C5 inhibitors, demonstrating iptacopan to be a more favourable treatment. These results were obtained to address the lack of data from C5 inhibitor treatments on haematological response and enable comparison with the single-arm, phase 3 APPOINT-PNH trial that investigated oral iptacopan monotherapy in complement inhibitor-naive patients with PNH [13]. These results also complement data from the phase 3 APPLY-PNH trial, in which C5 inhibitor-treated patients with persistent anaemia were randomised to iptacopan monotherapy or continue treatment with C5 inhibitors [13].

Advanced machine learning algorithms were used, concurrently using propensity score weights and an outcome model to estimate the treatment effect of C5 inhibitor therapy in the APPOINT-PNH trial cohort. The results showed that treatment with C5 inhibitors could lead to improvements in haemoglobin levels and transfusion avoidance in most patients; however, these improvements were not as large as those observed for iptacopan in the APPOINT-PNH trial. In the APPOINT-PNH trial, which enrolled C5 inhibitor treatment-naive patients, iptacopan treatment led to improvements in haemoglobin levels and transfusion avoidance in a larger proportion of patients. The endpoints reflecting improvement in anaemia are change from baseline in haemoglobin level of ≥ 2 g/dL, reaching a level of ≥ 12 g/dL (both in the absence of transfusions), transfusion avoidance and change from baseline in reticulocyte count. The lower bound of the 95% CIs of the primary (82.5) and secondary (47.5 for a haemoglobin level of ≥ 12 g/dL; 92.5 for transfusion avoidance) endpoints in the APPOINT-PNH trial was larger than the upper bound of the 95% CIs of these endpoints in the APPEX study (42.0 for a haemoglobin level of ≥ 2 g/dL; 21.1 for a haemoglobin level of ≥ 12 g/dL; 73.3 for transfusion avoidance). According to the World Health Organization, anaemia is defined as a haemoglobin concentration cutoff ranging from < 12 to <13 g/dL [23].

Mean haemoglobin levels increased over time for patients in both the APPEX and APPOINT-PNH cohorts, indicating a sustained treatment effect with both C5 inhibitors and iptacopan. However, the increase in haemoglobin levels occurred at an earlier timepoint in the APPOINT-PNH cohort than in the APPEX cohort. At Week 24, the mean haemoglobin level was lower in patients treated with C5 inhibitors (9.82 g/dL) than in those treated with iptacopan in the APPOINT-PNH trial (12.6 g/dL) [13]. The lower haemoglobin levels and the slower haemoglobin rise seen in the APPEX cohort reflect the presence of extravascular haemolysis associated with C5 inhibitor use, which is not seen with iptacopan use.

The ongoing open-label, multicentre roll-over extension programme is evaluating the long-term safety, tolerability and efficacy of iptacopan in patients with PNH over a 60-month period (NCT04747613) [24]. A post-hoc analysis of phase 3 trial data showed that patients treated with iptacopan experienced significant improvements in fatigue, health-related quality of life and disease-related symptoms [25]. In addition, a retrospective observational study of 1138 patients with PNH showed that lower haemoglobin concentrations were linked to higher hospitalisation rates, longer hospital stays and increased transfusion needs, with anaemia further exacerbating these risks [26]. LDH is a marker of intravascular haemolysis, and the results from this study indicate that iptacopan treatment in the APPOINT-PNH trial cohort led to a larger decrease in LDH levels than their predicted potential outcomes had they received C5 inhibitors. There is potentially an underestimation of the percent decrease from C5 inhibitor treatment because of the uncertainty in data collection in the real-world context, where measurements are not performed at regularly scheduled intervals, and because of the larger number of breakthrough haemolysis events in the retrieved databases. Several transfusion events in the APPEX cohort were triggered by breakthrough haemolysis events. However, despite the transfusions, the APPEX cohort did not achieve increased haemoglobin levels compared with those of the APPOINT-PNH cohort. In rare diseases such as PNH, when a clinical trial is uncontrolled, observational trials can provide benchmark information about endpoint achievement of standard-of-care treatments. The value of benchmark analysis, however, depends on the appropriateness of the methods, where the use of propensity score methods and causal comparisons is strengthened by clinical trial emulation methods in the design [27]. The use of a target trial framework in APPEX ensured that key aspects related to population, treatment and follow-up were similar. This minimised selection bias and confounding by design, ensuring that the treatment of events interfering with the interpretation of the estimates was handled similarly for both iptacopan and C5 inhibitors. Although this target trial emulation provides valuable insights into the comparison of iptacopan with C5 inhibitors, it does not diminish the importance of robust head-to-head comparative trials.

Our study has limitations. In a clinical trial, measurements are scheduled by protocol and do not depend on disease events; in a non-clinical trial setting, measurements can be either routine or motivated by clinical worsening. Thus, in the APPEX study database, the timeframe and frequency of assessments were irregular. To mitigate this limitation and include as many observations as possible, the endpoint assessment timeframe was extended from Days 126–168 post-index date to Days 100–200 after the index date, which was equivalent to Weeks 18–24 in the APPOINT-PNH trial. In addition, the endpoint results were determined by calculating the mean of all available values within the assessment window, instead of the strict use of scheduled visits in the APPOINT-PNH trial. This could have resulted in an overestimated proportion of responders when using clinical practice records, compared with that possibly observed if assessments had been regularly scheduled. Therefore, the adjusted estimate may not be optimal for a comparison of treatments

in APPEX to other treatments. Another possible limitation was the impact of assay variability, which was considered negligible because haematology measurements are standardised and were performed at reference hospitals. Other sources of uncertainty involved determination of baseline values for the APPEX cohort measurements, with the criteria differing from those used in the clinical trial. Missing baseline information from APPOINT-PNH was incorporated using multiple imputation, and patients with missing baseline information from APPEX were excluded from the analysis. Rubin's rule was applied to combine the results from each imputed APPOINT-PNH dataset. There were differences in the definition of breakthrough haemolysis events for APPEX compared with APPOINT-PNH (elevated LDH $\geq 2 \times$ upper limit of normal in the APPEX study vs. LDH $> 1.5 \times$ upper limit of normal in the APPOINT-PNH trial), which may have affected the reported rates of breakthrough haemolysis events. In addition, the C5 inhibitor crovalimab was not included in the study as it was not approved for PNH at the time the study was conducted. Finally, the cohorts differed in their regional representation. The APPOINT-PNH trial included 68% of patients from Asia [13], whereas all participants included in the APPEX study cohort were residents of European countries. Clinical trial data for treatment with C5 inhibitors indicated no clinically relevant differences in efficacy or safety between the Asian and European populations [28, 29]. Hence, these differences were considered as being of little relevance for the evaluation. Of note, target trials emulated using observational data are pragmatic because placebo controls and blinded outcomes are not possible in routine clinical practice; thus, observational data cannot emulate a placebo-controlled trial [17, 20, 22].

We considered the main sources of bias in our analyses, which were due to systematic differences in the data collection of outcomes, and we have described approaches to minimise those with any impact. In addition, the inclusion of age and sex in the final adjustment mitigated the potential for unmeasured confounding that may have been derived from covariates that were not considered for collection in the study protocol or covariates that were not available with sufficient completeness in all data sources and were, therefore, missing from the propensity score.

In conclusion, our results indicate that adult patients with PNH who have not received C5 inhibitor therapy may experience greater and sustained improvements in haematological response with iptacopan treatment than with C5 inhibitor treatment. Taken together, the results suggest that iptacopan monotherapy could potentially become a practice-changing, convenient outpatient treatment and a preferred therapeutic option for patients with haemolytic PNH.

Author Contributions

Substantial contribution to study conceptualisation or design: J. M. F. and M. D.; Data acquisition: M. H., R. J. K., M. D., I. B., L. M., F. S. F. and R. P. L.; Funding acquisition: J. M. F.; Conducted the research: R. J. K., J. M. F., I. B., L. M., F. S. F. and R. P. L.; Data analysis: R. J. K., J. M. F. and S. A.; Data interpretation: M. H., R. J. K., J. M. F. and M. D.; Supervision: J. M. F.; Visualisation: J. M. F. and S. A.; and writing (original draft preparation): J. M. F. and S. A. All authors participated in reviewing and editing of the manuscript and approved the final version.

Acknowledgements

We thank the patients and healthcare professionals who participated in the trials from which data for this study were generated. We gratefully acknowledge the contributions of Georgina Bermann whose scientific and analytical expertise were invaluable to the completion of this study. We thank Sophie Sun and Rima Izem for their contributions to statistical methods and analyses of APPEX. We thank Rina Vekaria Passmore, PhD (Novartis Global Business Solutions, London, UK), and Janis Noonan, PhD (Novartis Global Business Solutions, Dublin, Ireland), for medical editorial assistance with this manuscript in accordance with Good Publication Practice (GPP 2022) guidelines.

Conflicts of Interest

The authors declare no conflicts of interest

Data Availability Statement

Matthew Holt reports research funding from Sobi and support for congress travel from Alexion. Richard J. Kelly reports consultancy, research funding, and speaker fees from, and/or advisory board attendance for Alexion, Florio, Novartis Pharma AG, Otsuka, Sobi, and Roche. Jilles M. Fermont is an employee of, and an equity holder in, Novartis Pharma AG. Soudeh Ansari is an employee of, and an equity holder in, Novartis Pharma AG. Marion Dahlke is an employee of, and an equity holder in, Novartis Pharma AG. Isabelle Brindel has no conflicts of interest to report. Lynda Maafa has no conflicts of interest to report. Flore Sicre de Fontbrune reports consultancy for, and honoraria and/or research funding from, Alexion, Novartis Pharma AG, Pfizer, Samsung, Sobi, and Jazz Pharmaceuticals. Régis Peffault de Latour reports consultancy for, and honoraria and/or research funding from, Alexion, Amgen, F. Hoffman-La Roche, Merck Sharp and Dohme, Novartis Pharma AG, Pfizer, Samsung, and Sobi.

References

1. R. A. Brodsky, "Narrative Review: Paroxysmal Nocturnal Hemoglobinuria: The Physiology of Complement-Related Hemolytic Anemia," *Annals of Internal Medicine* 148, no. 8 (2008): 587–595.

2. C. Parker, M. Omine, S. Richards, et al., "Diagnosis and Management of Paroxysmal Nocturnal Hemoglobinuria," *Blood* 106, no. 12 (2005): 3699–3709.

3. A. M. Risitano, C. Frieri, E. Urciuoli, and L. Marano, "The Complement Alternative Pathway in Paroxysmal Nocturnal Hemoglobinuria: From a Pathogenic Mechanism to a Therapeutic Target," *Immunological Reviews* 313, no. 1 (2023): 262–278.

4. R. D. Cançado, A. D. Araújo, A. F. Sandes, et al., "Consensus Statement for Diagnosis and Treatment of Paroxysmal Nocturnal Haemoglobinuria," *Hematology, Transfusion and Cell Therapy* 43, no. 3 (2021): 341–348.

5. S. J. Richards, D. Painter, A. J. Dickinson, et al., "The Incidence and Prevalence of Patients With Paroxysmal Nocturnal Haemoglobinuria and Aplastic Anaemia PNH Syndrome: A Retrospective Analysis of the UK's Population-Based Haematological Malignancy Research Network 2004–2018," *European Journal of Haematology* 107, no. 2 (2021): 211–218.

6. A. Röth, J. Maciejewski, J. I. Nishimura, D. Jain, and J. I. Weitz, "Screening and Diagnostic Clinical Algorithm for Paroxysmal Nocturnal Hemoglobinuria: Expert Consensus," *European Journal of Haematology* 101, no. 1 (2018): 3–11.

7. F. Versino and B. Fattizzo, "Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria: From Biology to Therapy," *International Journal of Laboratory Hematology* 46, no. 1 (2024): 43–54.

8. P. Hillmen, N. S. Young, J. Schubert, et al., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," *New England Journal of Medicine* 355, no. 12 (2006): 1233–1243.

9. J. W. Lee, F. Sicre de Fontbrune, L. Wong Lee Lee, et al., "Ravulizumab (ALXN1210) vs Eculizumab in Adult Patients With PNH Naive to Complement Inhibitors: The 301 Study," *Blood* 133, no. 6 (2019): 530–539.

10. P. E. Debureaux, A. G. Kulasekararaj, F. Cacace, et al., "Categorizing Hematological Response to Eculizumab in Paroxysmal Nocturnal Hemoglobinuria: A Multicenter Real-Life Study," *Bone Marrow Transplantation* 56, no. 10 (2021): 2600–2602.

11. J. Fishman, S. Kuranz, M. M. Yeh, K. Brzozowski, and H. Chen, "Changes in Hematologic Lab Measures Observed in Patients With Paroxysmal Nocturnal Hemoglobinuria Treated With C5 Inhibitors, Ravulizumab and Eculizumab: Real-World Evidence From a US Based EMR Network," *Hematology Reports* 15, no. 2 (2023): 266–282.

12. H. Schrezenmeier, A. Kulasekararaj, L. Mitchell, et al., "One-Year Efficacy and Safety of Ravulizumab in Adults With Paroxysmal Nocturnal Hemoglobinuria Naive to Complement Inhibitor Therapy: Open-Label Extension of a Randomized Study," *Therapeutic Advances in Hematology* 11 (2020): 1–14.

13. R. Peffault de Latour, A. Roth, A. G. Kulasekararaj, et al., "Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria," *New England Journal of Medicine* 390, no. 11 (2024): 994–1008.

14. European Medicines Agency, "Reflection Paper on Use of Real-World Data in Non-Interventional Studies to Generate Real-World Evidence," accessed August 22, 2024, https://www.ema.europa.eu/system/files/documents/scientific-guideline/reflection-paper-real-world-evidence_draft-public-consultation_may_august_2024_en.pdf.

15. L. V. Hampson, J. F. Chu, A. Zia, et al., "Combining the Target Trial and Estimand Frameworks to Define the Causal Estimand: An Application Using Real-World Data to Contextualize a Single-Arm Trial," *Statistics in Biopharmaceutical Research* 16, no. 1 (2024): 1–10.

16. M. A. Hernan, B. C. Sauer, S. Hernandez-Diaz, R. Platt, and I. Shrier, "Specifying a Target Trial Prevents Immortal Time Bias and Other Self-Inflicted Injuries in Observational Analyses," *Journal of Clinical Epidemiology* 79 (2016): 70–75.

17. M. A. Hernán, W. Wang, and D. E. Leaf, "Target Trial Emulation a Framework for Causal Inference From Observational Data," *JAMA* 328, no. 24 (2022): 2446–2447.

18. H. Schmidli, D. A. Haring, M. Thomas, A. Cassidy, S. Weber, and F. Bretz, "Beyond Randomized Clinical Trials: Use of External Controls," *Clinical Pharmacology & Therapeutics* 107, no. 4 (2020): 806–816.

19. U.S. Food and Drug Administration, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products," 2023, https://www.fda.gov/media/164960/download.

20. M. A. Hernan and J. M. Robins, "Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available," *American Journal of Epidemiology* 183, no. 8 (2016): 758–764.

21. J. A. Labrecque and S. A. Swanson, "Target Trial Emulation: Teaching Epidemiology and Beyond," *European Journal of Epidemiology* 32, no. 6 (2017): 473–475.

22. A. A. Matthews, G. Danaei, N. Islam, and T. Kurth, "Target Trial Emulation: Applying Principles of Randomised Trials to Observational Studies," *BMJ* 378, (2022): e071108.

23. World Health Organization, "Guideline on Haemoglobin Cutoffs to Define Anaemia in Individuals and Populations," accessed May 20, 2024, https://www.who.int/publications/i/item/9789240088542.

24. ClinicalTrials.gov, "Long-Term Safety and Tolerability of Iptacopan in Patients With Paroxysmal Nocturnal Hemoglobinuria," accessed November 22, 2024, https://clinicaltrials.gov/study/NCT04747613.

25. A. M. Risitano, C. M. de Castro, B. Han, et al., "Patient-Reported Improvements in Fatigue and Health-Related Quality of Life in the Phase 3 Studies APPLY-PNH and APPOINT-PNH Evaluating the Use of Iptacopan in C5 Inhibitor-Treated and Treatment-Naïve Patients With Paroxysmal Nocturnal Hemoglobinuria," *Blood* 142 (2023): 487.

26. J. Shammo, J. Kim, M. Georget, T. Pattpaka, and J. M. Fermont, "P796: Hospitalization in Patients With Paroxysmal Nocturnal Hemoglobinuria: A Retrospective Analysis of Observational Study Data From the United States," *Hemasphere* 7 (2023): e22585a22582.

27. S. P. Forbes and I. J. Dahabreh, "Benchmarking Observational Analyses Against Randomized Trials: A Review of Studies Assessing Propensity Score Methods," *Journal of General Internal Medicine* 35, no. 5 (2020): 1396–1404.

28. European Medicines Agency, "Assessment Report Ultomiris. International Non-Proprietary Name: Ravulizumab," 2019, https://www.ema.europa.eu/documents/assessment-report/ultomiris-epar-public-assessment-report_en.pdf.

29. U.S. Food and Drug Administration. "BLA Multidisciplinary Review and Evaluation BLA 761108 Ultomiris (Ravulizumab)," 2018, https://www.fda.gov/media/135113/download.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.