ORIGINAL ARTICLE

Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria

R. Peffault de Latour, A. Röth, A.G. Kulasekararaj, B. Han, P. Scheinberg, J.P. Maciejewski, Y. Ueda, C.M. de Castro, E. Di Bona, R. Fu, L. Zhang, M. Griffin, S.M.C. Langemeijer, J. Panse, H. Schrezenmeier, W. Barcellini, V.A.Q. Mauad, P. Schafhausen, S. Tavitian, E. Beggiato, L.P. Chew, A. Gaya, W.-H. Huang, J.H. Jang, T. Kitawaki, A. Kutlar, R. Notaro, V. Pullarkat, J. Schubert, L. Terriou, M. Uchiyama, L. Wong Lee Lee, E.-S. Yap, F. Sicre de Fontbrune, L. Marano, F. Alashkar, S. Gandhi, R. Trikha, C. Yang, H. Liu, R.J. Kelly, B. Höchsmann, C. Kerloeguen, P. Banerjee, R. Levitch, R. Kumar, Z. Wang, C. Thorburn, S. Maitra, S. Li, A. Verles, M. Dahlke, and A.M. Risitano

ABSTRACT

BACKGROUND

Persistent hemolytic anemia and a lack of oral treatments are challenges for patients with paroxysmal nocturnal hemoglobinuria who have received anti-C5 therapy or have not received complement inhibitors. Iptacopan, a first-in-class oral factor B inhibitor, has been shown to improve hemoglobin levels in these patients.

METHODS

In two phase 3 trials, we assessed iptacopan monotherapy over a 24-week period in patients with hemoglobin levels of less than 10 g per deciliter. In the first, anti-C5–treated patients were randomly assigned to switch to iptacopan or to continue anti-C5 therapy. In the second, single-group trial, patients who had not received complement inhibitors and who had lactate dehydrogenase (LDH) levels more than 1.5 times the upper limit of the normal range received iptacopan. The two primary end points in the first trial were an increase in the hemoglobin level of at least 2 g per deciliter from baseline and a hemoglobin level of at least 12 g per deciliter, each without red-cell transfusion; the primary end point for the second trial was an increase in hemoglobin level of at least 2 g per deciliter from baseline without red-cell transfusion.

RESULTS

In the first trial, 51 of the 60 patients who received iptacopan had an increase in the hemoglobin level of at least 2 g per deciliter from baseline, and 42 had a hemoglobin level of at least 12 g per deciliter, each without transfusion; none of the 35 anti-C5–treated patients attained the end-point levels. In the second trial, 31 of 33 patients had an increase in the hemoglobin level of at least 2 g per deciliter from baseline without red-cell transfusion. In the first trial, 59 of the 62 patients who received iptacopan and 14 of the 35 anti-C5–treated patients did not require or receive transfusion; in the second trial, no patients required or received transfusion. Treatment with iptacopan increased hemoglobin levels, reduced fatigue, reduced reticulocyte and bilirubin levels, and resulted in mean LDH levels that were less than 1.5 times the upper limit of the normal range. Headache was the most frequent adverse event with iptacopan.

CONCLUSIONS

Iptacopan treatment improved hematologic and clinical outcomes in anti-C5–treated patients with persistent anemia — in whom iptacopan showed superiority to anti-C5 therapy — and in patients who had not received complement inhibitors. (Funded by Novartis; APPLY-PNH ClinicalTrials.gov number, NCT04558918; APPOINT-PNH ClinicalTrials.gov number, NCT04820530.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Prof. Peffault de Latour can be contacted at regis.peffaultdelatour@aphp.fr or at the French Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Université de Paris, Saint-Louis Hospital, 1 Ave. Claude Vellefaux, 75010 Paris, France. Prof. Risitano can be contacted at amrisita@unina.it or at Ematologia e Trapianto Emopoietico, Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati, Contrada Amoretta 83100, Avellino, Italy.

Profs. Peffault de Latour and Risitano and Drs. Röth, Kulasekararaj, Han, and Scheinberg contributed equally to this article.

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CME

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by hemolysis, thrombosis, and bone marrow failure.[1] PNH is caused by the expansion of hematopoietic stem cells carrying a somatic mutation in *PIGA*, which encodes phosphatidylinositol N-acetylglucosaminyltransferase, subunit A.[2] Affected red cells lack surface glycosylphosphatidylinositol-linked complement regulators CD55[3] and CD59,[4] which renders them susceptible to complement activation leading to intravascular hemolysis (Fig. S1A in the Supplementary Appendix, available with the full text of this article at NEJM.org).[5,6]

Intravenous anti-C5 monoclonal antibodies became the standard treatment for hemolytic PNH in 2007 after eculizumab led to intravascular hemolysis control (with hemoglobin stabilization in approximately half the patients),[7-9] reduced thromboembolic risk,[10] and improved long-term survival.[11,12] Ravulizumab, a long-acting eculizumab derivative administered every 8 weeks (instead of every 2 weeks), has shown similar efficacy.[13] However, many patients continue to have anemia despite anti-C5 therapy,[7,8,14-16] mainly because of ongoing activation of the proximal complement pathways that leads to opsonization of PNH red cells with C3 fragments and elimination by macrophages in the spleen and liver (extravascular hemolysis) (Fig. S1B).[15,17-21] These observations led to the development of proximal complement inhibitors,[9,22,23] including the anti-C3 agent pegcetacoplan.[24,25]

Iptacopan is an oral proximal complement inhibitor that targets factor B in the alternative pathway (Fig. S1C).[26-29] In phase 2 trials, iptacopan abrogated extravascular hemolysis and maintained intravascular hemolysis control in patients with PNH and persistent anemia despite anti-C5 treatment[28] and controlled intravascular hemolysis without causing extravascular hemolysis in patients who had not received a complement inhibitor in the 3 months before trial entry.[29]

We report the primary efficacy and safety data of iptacopan from the 24-week core treatment periods in two phase 3, open-label trials: APPLY-PNH, a randomized trial involving patients with PNH who had persistent anemia despite anti-C5 treatment, and APPOINT-PNH, a single-group trial involving patients with hemolytic PNH who had not previously received complement inhibitor therapy.

Methods

Patients

Both trials enrolled patients 18 years of age or older with PNH (confirmed by affected red-cell and white-cell populations of at least 10% of the total corresponding counts, detected by flow cytometry), with mean hemoglobin levels of less than 10 g per deciliter and with no laboratory evidence of bone marrow failure. In the APPLY-PNH trial, patients had received eculizumab (Soliris) or ravulizumab (Ultomiris) in a stable regimen for at least 6 months before randomization. Patients in the APPOINT-PNH trial who had not received complement-inhibitor therapy had lactate dehydrogenase (LDH) levels that were more than 1.5 times the upper limit of the normal range. All the patients provided written informed consent. See the Supplementary Methods section in the Supplementary Appendix for a list of inclusion and exclusion criteria.

A Quick Take is available at NEJM.org

Trial Design and Oversight

Both trials included an 8-week screening period, a 24-week core treatment period, and a 24-week extension period (Fig. S2). In the APPLY-PNH trial, patients were randomly assigned in an 8:5 ratio, by means of an interactive response system, to receive oral iptacopan monotherapy or to continue anti-C5 therapy. Randomization was stratified according to anti-C5 therapy (eculizumab or ravulizumab) and whether a red-cell transfusion had been received in the preceding 6 months (yes or no). Iptacopan was administered by the patients at a dose of 200 mg twice daily in both trials; anti-C5 therapy was administered intravenously according to the therapy received (i.e., every 2 weeks for patients receiving eculizumab and every 8 weeks for patients receiving ravulizumab).

Patients were enrolled in the APPLY-PNH trial at 39 sites in 12 countries and in the APPOINT-PNH trial at 12 sites in 8 countries. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Institutional review boards at each center approved the protocols (available at NEJM.org). The sponsor, Novartis, designed the trials with input from steering committees that included some of the academic authors (six authors in the APPLY-PNH trial and five in the APPOINT-

PNH trial). The investigators gathered the data, which were analyzed by the sponsor. The first and last authors wrote the first draft of the manuscript. All the authors and the sponsor contributed to subsequent drafts, with medical writing assistance funded by the sponsor. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trials to the protocols. All the authors signed data confidentiality agreements. The sponsor provided iptacopan; anti-C5 therapy was provided by the sites or the sponsor.

END POINTS

The two primary end points of the APPLY-PNH trial were an increase in hemoglobin level of at least 2 g per deciliter from baseline and a hemoglobin level of at least 12 g per deciliter (both as measured on at least three of four assessments between days 126 and 168 [day 1 was the day of the first dose], a time frame chosen to allow investigation of a durable hematologic response and to show the actual treatment effect of iptacopan or anti-C5), each without red-cell transfusions between days 14 and 168 or without meeting the protocol-specified criteria for red-cell transfusion. In the APPOINT-PNH trial, an increase in hemoglobin of at least 2 g per deciliter from baseline without red-cell transfusion was the primary end point, and a hemoglobin level of at least 12 g per deciliter without red-cell transfusion was a secondary end point. (The assessment time frame and definitions of these end points were the same as those in the APPLY-PNH trial.) Secondary end points in both trials were transfusion avoidance (defined as not receiving red-cell transfusions and not meeting the protocol-specified criteria for transfusion between days 14 and 168); changes from baseline in the hemoglobin level, scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) survey, and the absolute reticulocyte count; the percentage change from baseline in the LDH level (with each end point of change from baseline assessed using the model-adjusted mean of four visits [on days 126, 140, 154, and 168]); occurrences of clinical breakthrough hemolysis (defined by meeting one of the two clinical criteria [decrease in hemoglobin level ≥2 g per deciliter or PNH symptoms of gross hemoglobinuria, hemolytic crisis, dysphagia, or any other clinically significant sign or symptom associated with PNH] in addition to elevated LDH level [>1.5 times the upper limit of the normal range]); major adverse vascular events; and safety (all assessed between days 1 and 168). See the Supplementary Methods section for a list of the exploratory end points.

STATISTICAL ANALYSIS

Efficacy and safety were assessed in all the patients. The APPLY-PNH trial was designed to show the superiority of iptacopan over anti-C5 therapy; the overall type I error was controlled at the one-sided 2.5% level. Superiority was determined with the use of a sequentially rejective testing procedure to adjust for multiplicity in the primary and secondary end points (Fig. S3). Unadjusted one-sided P values are shown for end points in which superiority was shown (unadjusted and adjusted one-sided P values for all end points are shown in Table S1 in the Supplementary Appendix). The primary end points in the APPLY-PNH trial were assessed by calculation of odds ratios, estimated (or marginal) proportions, and differences in estimated proportions with the use of a logistic-regression model with a Firth correction that adjusted for treatment and randomization strata and with baseline covariates (i.e., sex, age ≥45 years, and hemoglobin level of ≥9 g per deciliter at baseline) as factors.

The primary end point in the APPOINT-PNH trial was assessed by means of derivation of an estimated proportion (the simple proportion of persons who had a response from multiple imputed data sets), with 95% confidence intervals computed with the use of bootstrap analysis. The lower boundary of the two-sided 95% confidence interval was compared with a prespecified threshold of 15%, which was derived by indirectly estimating hemoglobin responses in two trials of C5 inhibitors.[8,30] Estimated proportions reflect the probability that the end-point criteria were met in the trial populations. See the Supplementary Methods section for details of the statistical methods.

RESULTS

TRIAL POPULATIONS

The APPLY-PNH trial began on January 25, 2021 (data-cutoff date, September 26, 2022); 97 patients with persistent anemia (out of 125 who underwent screening) received iptacopan (62 patients) or continued anti-C5 therapy (35 patients) for 24 weeks

(Fig. S4). The mean baseline hemoglobin level was 8.9 g per deciliter. A total of 58% of the patients had received transfusions within 6 months before undergoing randomization (Table 1 and Table S2).

The APPOINT-PNH trial began on July 19, 2021 (data-cutoff date, November 2, 2022); 40 patients who had not undergone complement inhibitor therapy (out of 52 who underwent screening) received iptacopan for 24 weeks (Fig. S5). At baseline, the mean hemoglobin level was 8.2 g per deciliter, and the mean LDH level was 1698.8 U per liter. A total of 70% of the patients had received transfusions in the 6 months before they received trial treatment (Table 1). Adherence to the iptacopan regimen, assessed according to the mean relative dose intensity, was 99.6% in the APPLY-PNH trial and 99.4% in the APPOINT-PNH trial (Table S3). The representativeness of the trial populations is shown in Table S4.

HEMOGLOBIN AND TRANSFUSION-AVOIDANCE EFFICACY END POINTS

In the APPLY-PNH trial, iptacopan was superior to anti-C5 therapy with regard to both primary end points. A total of 51 of 60 evaluable patients who received iptacopan (a response could not be unequivocally established for 2 of the 62 patients assigned to the iptacopan group owing to partial missing data between days 126 and 168) (Table S5 and Fig. S6A) had an increase in the hemoglobin level of at least 2 g per deciliter from baseline without red-cell transfusions, as compared with none of the 35 patients who received anti-C5 therapy; estimated percentages, 82% (95% confidence interval [CI], 73 to 90) and 2% (95% CI, 1 to 4), respectively (difference, 80 percentage points [95% CI, 71 to 88]; P<0.001) (Fig. 1A). A total of 42 of 60 evaluable patients who received iptacopan had a hemoglobin level that reached at least 12 g per deciliter without red-cell transfusion, as compared with none of the 35 patients treated with anti-C5; estimated percentages, 69% (95% CI, 58 to 79) and 2% (95% CI, 1 to 4), respectively, (difference, 67 percentage points [95% CI, 56 to 77]; P<0.001) (Fig. 1B).

A total of 31 of the 33 evaluable patients in the APPOINT-PNH trial had an increase in hemoglobin level of at least 2 g per deciliter from baseline without red-cell transfusions; estimated percentage, 92% (95% CI, 82 to 100), exceeding the 15% threshold (Fig. 1C); a response could not be unequivocally established for 7 of the patients, owing to partial missing data between days 126 and 168 (Fig. S6B). A total of 19 of 33 evaluable patients had hemoglobin levels that reached at least 12 g per deciliter without red-cell transfusions; estimated percentage, 63% (95% CI, 48 to 78) (Fig. 1D). Results from a prespecified sensitivity analysis are shown in Figure S7.

In the APPLY-PNH trial, the adjusted least-squares mean hemoglobin change from baseline was 3.6 g per deciliter (95% CI, 3.3 to 3.9) for iptacopan as compared with −0.06 g per deciliter (95% CI, −0.5 to 0.3) for anti-C5 (difference, 3.7 g per deciliter [95% CI, 3.2 to 4.1]; P<0.001). The 24-week mean hemoglobin levels, irrespective of red-cell transfusions, were 12.6 g per deciliter in the iptacopan group and 9.2 g per deciliter in the anti-C5 group (Fig. 2A). In the APPOINT-PNH trial, the adjusted least-squares mean hemoglobin change from baseline was 4.3 g per deciliter (95% CI, 3.9 to 4.7); the 24-week mean hemoglobin level was 12.6 g per deciliter (Fig. 2B).

Between days 14 and 168 of the APPLY-PNH trial, 59 of 62 patients who received iptacopan and 14 of 35 patients who received anti-C5 met the criteria for transfusion avoidance; estimated percentages, 95% (95% CI, 88 to 100) and 26% (95% CI, 12 to 42), respectively (difference, 69 percentage points [95% CI, 51 to 84]; P<0.001) (Fig. 2C and Fig. S8A). Results from a post hoc sensitivity analysis were consistent with those from the prespecified analysis (Fig. S9). No patients in the APPOINT-PNH trial received a transfusion or met the criteria for receiving a transfusion between days 14 and 168; estimated percentage, 98% (95% CI, 92 to 100) (Fig. 2D and Fig. S8B).

OTHER EFFICACY END POINTS

In the APPLY-PNH trial, the adjusted least-squares mean change from baseline in the FACIT-Fatigue score (ranging from 0 to 52, with higher scores indicating less fatigue) was 8.6 points (95% CI, 6.7 to 10.5) for iptacopan and 0.3 points (95% CI, –2.2 to 2.8) for anti-C5 (difference, 8.3 points [95% CI, 5.3 to 11.3]; P<0.001) (Fig. 3A). In the APPOINT-PNH trial, the adjusted least-squares mean change from baseline in the FACIT-Fatigue score was 10.8 points (95% CI, 8.7 to 12.8) (Fig. 3B).

In the APPLY-PNH trial, we found no evidence of a between-group difference in the adjusted mean percentage change from baseline in the LDH

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	APPLY-PNH†		APPOINT-PNH
	Anti-C5 therapy (N=35)	Iptacopan (N=62)	Iptacopan (N=40)
Age — yr	49.8±16.7	51.7±16.9	42.1±15.9
Female sex — no. (%)	24 (69)	43 (69)	17 (42)
Race — no. (%)‡			
White	26 (74)	48 (77)	12 (30)
Asian	7 (20)	12 (19)	27 (68)
Black	2 (6)	2 (3)	1 (2)
Body-mass index§			
Mean	26.9±6.3	24.9±5.0	24.7±3.3
Median (range)	25.2 (16.2–51.1)	23.5 (17.7–39.4)	24.4 (18.9–35.7)
Time since diagnosis — yr	13.5±10.9	11.9±9.8	4.7±5.5
Mean duration of anti-C5 therapy — yr	4.2±3.9	3.8±3.6	NA
Anti-C5 therapy in the 6 mo before randomization — no. (%)			
Eculizumab	23 (66)	40 (65)	NA
Ravulizumab	12 (34)	22 (35)	NA
Red-cell transfusions¶			
No. of patients (%)	21 (60)	35 (56)	28 (70)
Mean no. of transfusions	4.0±4.3	3.1±2.6	3.1±2.1
Median no. of transfusions (range)	2 (1–19)	2 (1–13)	2 (1–8)
Hemoglobin — g/dl‖			
Mean	8.9±0.9	8.9±0.7	8.2±1.1
Median (range)	9.0 (6.2–9.9)	9.0 (6.8–10.0)	8.1 (5.8–10.0)
FACIT-Fatigue score‖			
Mean	30.8±11.5	34.7±9.8	32.8±10.2
Median (range)	32 (10–50)	35 (11–52)	34.3 (13–51)
Absolute reticulocyte count — $\times 10^{-9}$/liter‖			
Mean	190.6 (80.9)	193.2 (83.6)	154.3 (63.7)
Median (range)	160 (90–412)	177 (51–563)	139 (59–325)
LDH — U/liter‖			
Mean	272.7±84.8	269.1±70.1	1698.8±683.3
Median (range)	261 (133–562)	268 (150–539)	1582 (522–3244)
LDH >1.5×ULN — no. (%)‖	3 (9)	4 (6)	40 (100)
Total bilirubin — μmol/liter‖**			
Mean	31.8±20.3	31.6±30.5	28.7±14.9
Median (range)	28 (6–106)	25 (7–169)	27 (8–78)
Total PNH red-cell population size — %‖††			
Mean	57.4±29.7	64.6±27.5	42.7±21.2
Median (range)	52.8 (9.8–99.4)	66.0 (10.6–99.9)	40.3 (9.0–92.9)

Table 1. (Continued.)

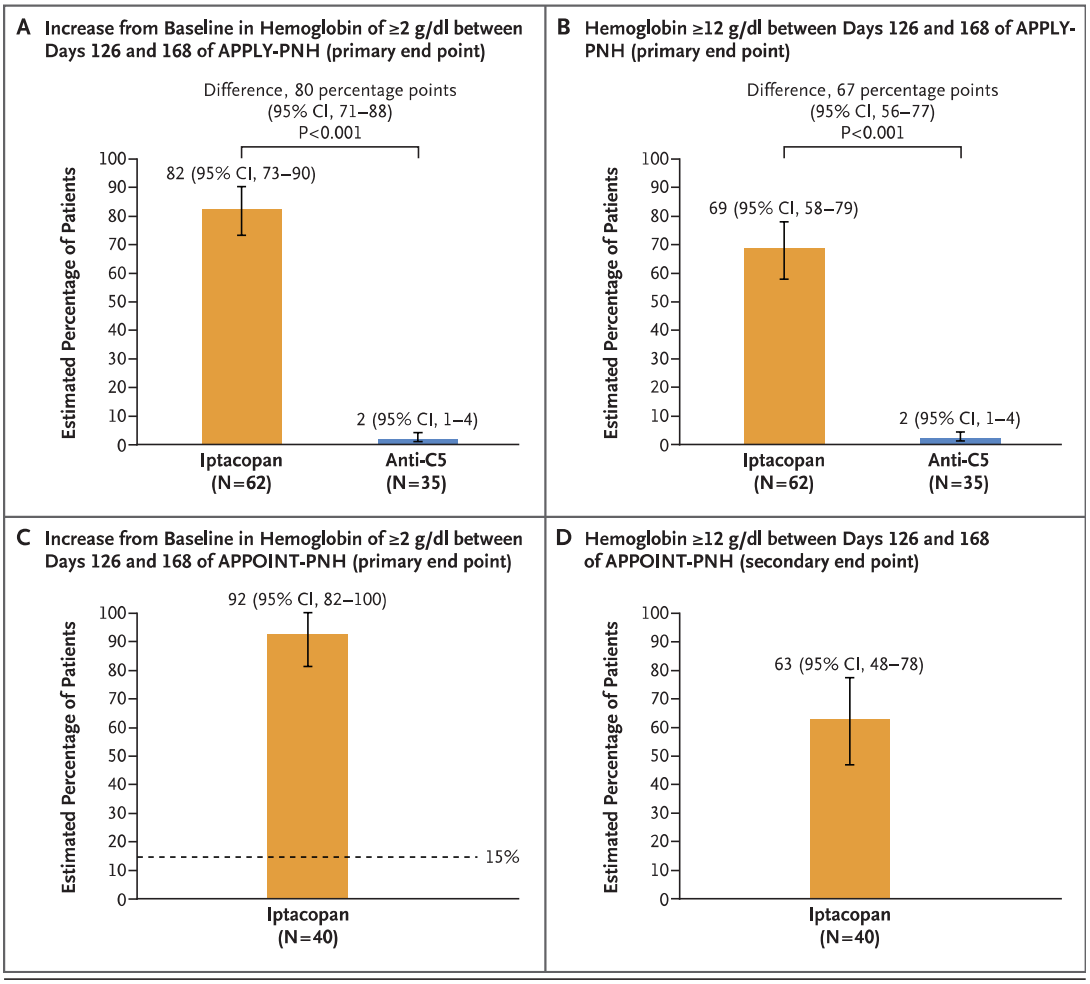
Characteristic	APPLY-PNH†		APPOINT-PNH
	Anti-C5 therapy (N=35)	Iptacopan (N=62)	Iptacopan (N=40)
C3d+ PNH red cells — %‖††			
Mean	17.5±12.2	19.2±16.1	0.7±0.4
Median (range)	14.2 (1.8–51.2)	14.5 (0.0–71.8)	0.6 (0.1–1.9)
Total PNH granulocyte population size — %‖††			
Mean	93.1±7.9	94.4±8.8	86.1±18.6
Median (range)‡‡	96.2 (65.8–100.0)	98.1 (56.5–100.4)	92.5 (1.0–99.5)
History of major adverse vascular events — no. (%)	10 (29)	12 (19)	5 (12)
History of ≥1 event of aplastic anemia— no. (%)	5 (14)	9 (15)	16 (40)

* Plus–minus values are means ±SD. LDH denotes lactate dehydrogenase, NA not applicable, PNH paroxysmal nocturnal hemoglobinuria, and ULN upper limit of the normal range.
† The 24-week data are derived from the final data sets at trial completion; 24-week data previously reported in congress abstracts were from interim data sets generated while the trials were ongoing (at which point the databases were still live); therefore, minor numerical differences exist between the final 24-week efficacy data reported here and the previously reported 24-week efficacy data.
‡ Race was reported by the patients. In the APPOINT-PNH trial, 22 patients (55%) were Chinese, 3 (8%) were Korean, and 2 (5%) were Malaysian.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Shown are data from patients who received transfusions of red cells in the 6 months before randomization in the APPLY-PNH trial and in the 6 months before the receipt of trial treatment in the APPOINT-PNH trial.
‖ Baseline values were defined as the last result obtained at or before the start of the trial treatment (day 1), except for the baseline hemoglobin level, which was defined as the mean of two measurements obtained during the screening period (for any patients who received a red-cell transfusion during screening after the first confirmatory hemoglobin measurement, the baseline is the first measurement). Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scale range from 0 to 52, with higher scores indicating less fatigue.
** To convert bilirubin to milligrams per deciliter, divide by 17.1.
†† Inclusion criteria for both trials included a PNH red-cell (type II + III) and a granulocyte or monocyte population size of at least 10%; PNH granulocyte population size in the lower range (<10%) is unlikely to be associated with meaningful hemolysis and is not an indication for treatment.
‡‡ In the analysis of flow cytometry results in the APPLY-PNH trial, gating of the granulocyte population overlapped slightly (which was not visible during the measurement), and some cells may have been counted twice, resulting in a maximum range value for the iptacopan group that was slightly greater than 100%.

level (–3.5% [95% CI, –10.0 to 3.4] for iptacopan and –2.4% [95% CI, –10.8 to 6.7] for anti-C5) (Fig. 3C). In the APPOINT-PNH trial, the adjusted mean percentage change from baseline in the LDH level was –83.6% (95% CI, –84.9 to –82.1) (Fig. 3D); the 24-week mean and median LDH levels were 261.3 U per liter and 255.0 U per liter, respectively, with 95% of patients having LDH levels that were no greater than 1.5 times the upper limit of the normal range.

In the APPLY-PNH trial, the adjusted least-squares mean change from baseline in the absolute reticulocyte count was –115.8 (95% CI, –126.4 to –105.2) in the iptacopan group and 0.3×10^9 per liter (95% CI, –13.0 to 13.7) in the anti-C5 group (difference, -116.2×10^9 per liter [95% CI, 132.0 to –100.3]; P<0.001) (Fig. S10A). In the APPOINT-PNH trial, the adjusted least-squares mean change from baseline in the absolute reticulocyte count was -82.5×10^9 per liter (95% CI, –89.3 to –75.6) (Fig. S10B).

At week 24 of the APPLY-PNH trial, the mean (±SE) total bilirubin was 12.5±1.3 μmol per liter (0.73±0.08 mg per deciliter) with iptacopan as compared with 31.4±5.3 μmol per liter (1.84±0.31 mg per deciliter) with anti-C5 (mean change



from baseline, –18.9±3.0 vs. –0.5±3.9 μmol per liter [–1.11±0.18 vs. –0.03±0.23 mg per deciliter]) (Fig. S11A). The mean total bilirubin at week 24 of the APPOINT-PNH trial was 10.7±0.8 μmol per liter (0.63±0.05 mg per deciliter) (mean change from baseline, –18.1±2.1 μmol per liter [–1.06±0.12 mg per deciliter]) (Fig. S11B). In the APPLY-PNH trial, the mean total PNH red-cell (type II + type III) population size at week 24 was 93.2±1.4% for iptacopan as compared with 59.7±4.6% for anti-C5 (mean change from baseline, 28.6±3.1% vs. 4.3±3.8%) (Fig. S12A). At week 24, a mean of 0.3±0.2% and 13.5±1.7% of PNH red cells were C3d+ in the iptacopan and anti-C5 groups, respectively (mean change from baseline, –19.3±2.3% vs. –4.5±2.0%) (Fig. S13A). In the APPOINT-PNH trial, the mean total PNH red-cell population size was 87.1±1.6% at week 24 (mean change from baseline, 43.2±3.1%) (Fig. S12B), and C3d+ PNH red cells did not emerge; the mean percentage of C3d+ PNH red cells was consistently less than 1% (Fig. S13B). The PNH red-cell populations increased to sizes similar to those of the granulocyte populations in both trials (Fig. S14).

BREAKTHROUGH HEMOLYSIS AND MAJOR ADVERSE VASCULAR EVENTS

In the APPLY-PNH trial, 2 of the 62 patients who received iptacopan, as compared with 6 of the 35 patients who received anti-C5, had clinical breakthrough hemolysis events; the adjusted annualized rates were 0.1 (95% CI, 0.0 to 0.3) and 0.7 (95% CI, 0.3 to 1.7), respectively (annualized rate ratio of iptacopan vs. anti-C5, 0.1 [95% CI, 0.0 to 0.6; P=0.006). One major adverse vascular event (transient ischemic attack) was reported in the APPLY-PNH iptacopan group (adjusted annualized rate, 0.0 [95% CI, 0.0 to 0.3]) as compared with no major adverse vascular events with anti-C5.

Figure 1 (facing page). Estimated (Marginal) Proportion of Patients with Hematologic Responses in the 24-Week Core Treatment Periods of the APPLY-PNH and APPOINT-PNH Trials.

Panel A shows the estimated proportion of patients in the two groups in the APPLY-PNH trial who had an increase in the hemoglobin level of at least 2 g per deciliter from baseline between days 126 and 168 in the absence of red-cell transfusions between days 14 and 168. Panel B shows the estimated proportion of patients in the APPLY-PNH trial who had a hemoglobin level of at least 12 g per deciliter between days 126 and 168 in the absence of red-cell transfusions between days 14 and 168. Estimated proportions were calculated with the use of a logistic-regression model with adjustment for baseline covariates. The Firth correction was applied to the analyses, which accounted for the possibility of no patients in the anti-C5 group meeting the primary end-point criteria; consequently, the treatment effect of iptacopan is underestimated and the treatment effect of anti-C5 therapy is overestimated. For 2 of 62 patients, hematologic response could not be unequivocally established owing to partial missing data from the central laboratory regarding hemoglobin levels between days 126 and 168 and those patients were therefore not evaluable in the analysis of observed data. However, the missing data were modeled with the use of a multiple imputation framework; therefore, the estimated (marginal) responses shown in Panels A and B are based on the totality of data from the 62 patients. The 24-week data are derived from the final data sets at trial completion. After the 24-week interim database lock in the APPLY-PNH trial (at which point the database was still live), we confirmed that an additional red-cell transfusion was administered in the iptacopan group during the 24-week period; therefore, minor numerical differences exist between the final 24-week efficacy data reported here and the previously reported 24-week efficacy data. Panel C shows the estimated percentage of patients who had an increase in the hemoglobin level of at least 2 g per deciliter from baseline between days 126 and 168 in the absence of red-cell transfusions between days 14 and 168 in the APPOINT-PNH trial. The dashed line indicates the derived 15% threshold, which was exceeded by a factor of more than five. We analyzed the primary end point by deriving an estimated proportion as the simple proportion of patients with a response from all imputed data sets, with 95% confidence intervals computed with the use of bootstrap analysis. Panel D shows the estimated percentage of patients who had a hemoglobin level of at least 12 g per deciliter between days 126 and 168 in the absence of red-cell transfusions administered between days 14 and 168 in the APPOINT-PNH trial. This secondary end point was analyzed with the use of methods similar to those used for analysis of the primary end point. Hematologic response could not be unequivocally established for 7 patients owing to partial missing data from the central laboratory regarding hemoglobin levels between days 126 and 168 and was therefore not evaluable in the analysis of observed data. However, the missing data were modeled with the use of a multiple-imputation framework; therefore, the estimated (marginal) responses shown in Panels C and D are based on the totality of data from the 40 patients. In all panels, I bars indicate 95% confidence intervals.

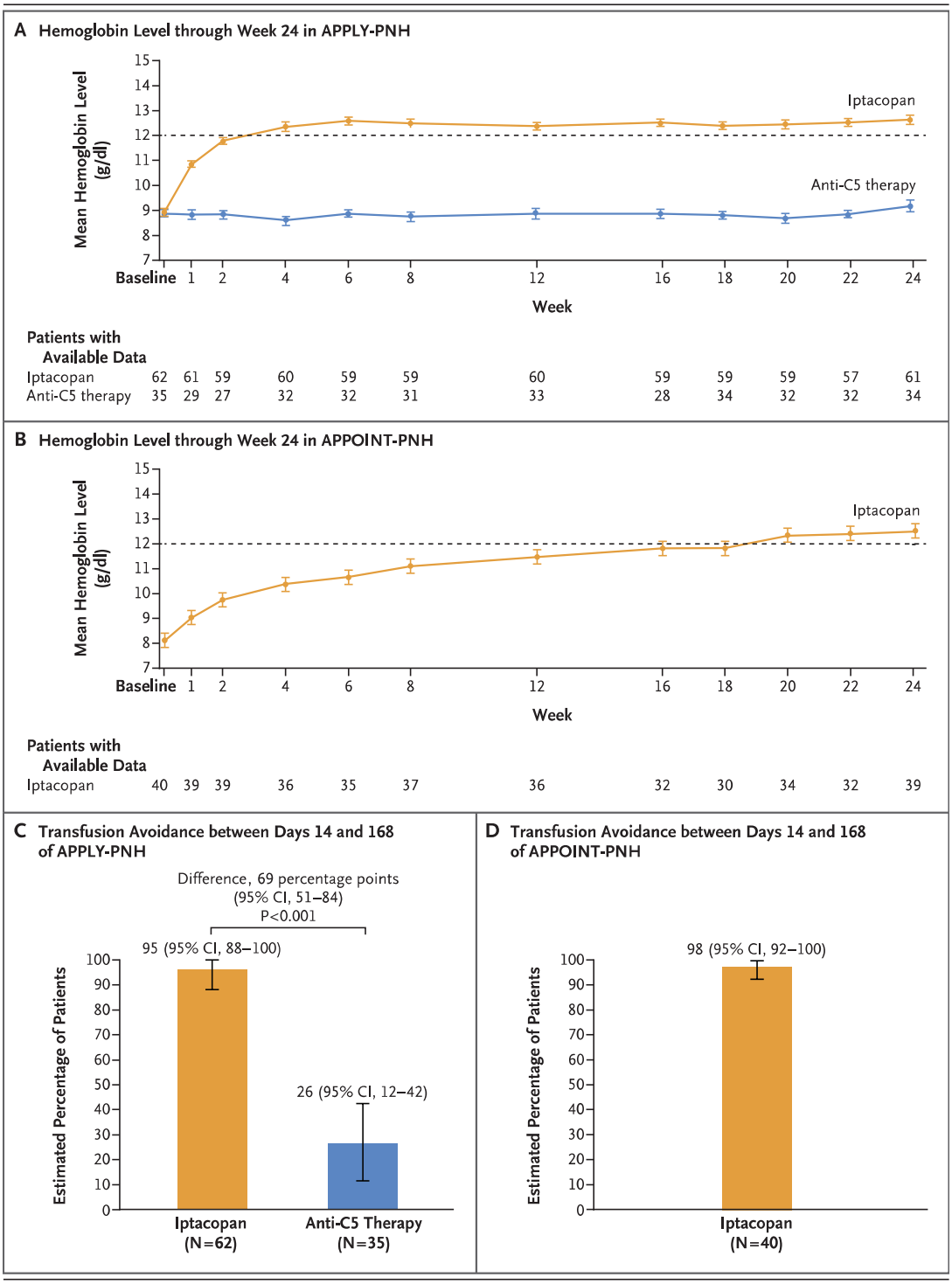
(See the Supplementary Methods section for a description of major adverse vascular events.) In the APPOINT-PNH trial, no patients had clinical breakthrough hemolysis or major adverse vascular events (adjusted annualized rate for both end points, 0.0 [95% CI, 0.0 to 0.2]).

In both trials, clinical breakthrough hemolysis and major adverse vascular events were reported as adverse events that occurred during treatment. In the APPLY-PNH trial, two patients who received iptacopan had breakthrough hemolysis adverse events (1 mild and 1 moderate event; the moderate event was suspected, but not confirmed, to be partially attributable to concomitant immune-mediated hemolysis) as compared with six patients who received anti-C5 (11 events: 2 mild, 8 moderate, and 1 severe). An additional two patients who received anti-C5 treatment had extravascular hemolysis adverse events (Table S7). In the anti-C5 group, 1 breakthrough hemolysis event and 1 extravascular hemolysis event met the prespecified criteria for serious events. In the APPOINT-PNH trial, no hemolysis adverse events were noted. The transient ischemic attack that was reported in the APPLY-PNH trial was considered by the investigator to be unrelated to iptacopan and may have been a result of a concomitant serious adverse event of sinus-node dysfunction (sick sinus syndrome) (see the Supplementary Results section).

SAFETY

No deaths were noted, and no adverse events led to treatment discontinuation in either trial. One patient in the APPLY-PNH trial discontinued iptacopan because of pregnancy (see the Supplementary Results section); no patients in the APPOINT-PNH trial discontinued iptacopan. Serious adverse events were reported in 10% of the patients who received iptacopan and in 14% of the patients who received anti-C5 treatment in the APPLY-PNH trial, and in 10% of the patients in the APPOINT-PNH trial (Table S8).

In the APPLY-PNH trial, nonserious adverse events that occurred more frequently with iptacopan than with anti-C5 were headache (in 16% of patients with iptacopan vs. 3% of patients



with anti-C5), diarrhea (in 15% vs. 6%), nasopharyngitis (in 11% vs. 6%), and nausea (in 10% vs. 3%). Coronavirus disease 2019 (Covid-19; in 8% vs. 26%) and breakthrough hemolysis (in 3% vs. 17%) occurred more frequently with anti-C5 (Table 2 and Table S9). In the APPLY-PNH trial, headache, diarrhea, and nausea were not severe with iptacopan; most cases were not suspected

Figure 2 (facing page). Hemoglobin Levels and Transfusion Avoidance during the 24-Week Core Treatment Periods of the APPLY-PNH and APPOINT-PNH Trials.

Panel A shows the mean hemoglobin level, irrespective of red-cell transfusions, from baseline to week 24 in the two groups in the APPLY-PNH trial. Included are data from patients after they had received red-cell transfusions. The dashed line indicates a hemoglobin level of 12 g per deciliter, which was the threshold for meeting one of the two primary end points (without red-cell transfusions between days 14 and 168). The mean hemoglobin level of patients in the iptacopan group increased to more than 12 g per deciliter at week 4 and was maintained at that level throughout the trial. (Panel A adapted with permission from the American Society of Hematology, 2022.) Panel B shows the mean level of hemoglobin, irrespective of red-cell transfusions, from baseline to week 24 of the APPOINT-PNH trial. Included are data from patients after they had received red-cell transfusions. The mean hemoglobin level increased within the first week and continued to rise until week 16, when it began to plateau. The dashed line indicates a hemoglobin level of 12 g per deciliter, which was the threshold for meeting one of the secondary end points (without red-cell transfusions between days 14 and 168). In Panels A and B, I bars indicate standard error of the mean. Panel C shows the estimated percentage of the patients in the APPLY-PNH trial who did not receive red-cell transfusions or did not meet the criteria for red-cell transfusion (hemoglobin level, ≤9 g per deciliter with clinical signs or symptoms [or both] of sufficient severity to warrant a red-cell transfusion or ≤7 g per deciliter regardless of the presence of clinical signs or symptoms [or both]) between days 14 and 168. Three of 62 patients in the iptacopan group and 21 of 35 patients in the anti-C5 group received transfusions or met the criteria for red-cell transfusions between days 14 and 168. Estimated proportions were calculated with the use of a logistic-regression model with adjustment for baseline covariates. The 24-week data are derived from the final data sets at trial completion; 24-week data previously reported in congress abstracts were from interim data sets generated while the trials were ongoing. After the 24-week interim database lock of the APPLY-PNH trial (at which point the database was still live), we confirmed that another red-cell transfusion was administered in the iptacopan group during the 24-week period; therefore, minor numerical differences exist between the final 24-week efficacy data reported here and the previously reported 24-week efficacy data. Panel D shows the estimated proportion of patients who did not have red-cell transfusions or did not meet the criteria for red-cell transfusions (hemoglobin level, ≤9 g per deciliter [≤8 g per deciliter for patients in China] with clinical signs or symptoms [or both] of sufficient severity to warrant a red-cell transfusion or ≤7 g per deciliter [≤6 g per deciliter for patients in China] regardless of the presence of clinical signs or symptoms [or both]) between days 14 and 168 of the APPOINT-PNH trial. This secondary end point was analyzed with the use of methods similar to those used for analysis of the primary end point. The estimated percentage is less than 100% because central-laboratory data on the hemoglobin levels of 1 patient from China were intermittently missing and were consequently imputed; because some imputed values did not exceed 8 g per deciliter, the patient was considered to have met the criteria for transfusion on the basis of those imputed data sets even though no transfusion was administered. In panels C and D, I bars indicate 95% confidence intervals.

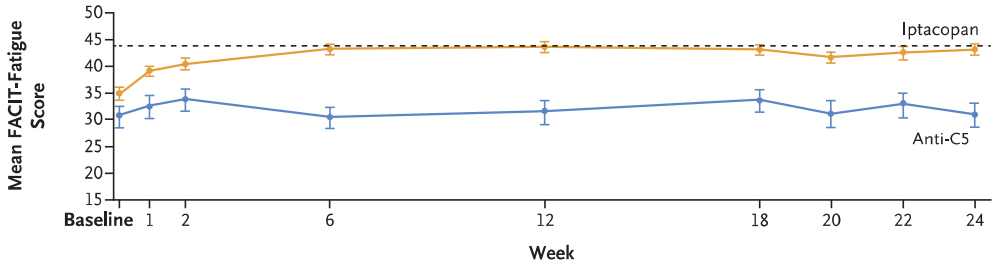
by the investigators to be related to iptacopan and resolved within 1 week after onset. In the APPOINT-PNH trial, the most common adverse events (occurring in ≥4 patients) were headache (in 28%), Covid-19 (in 15%), and upper respiratory tract infection (in 13%). None of the headaches were severe, and all resolved within 1 week after onset.

No meningococcal or pneumococcal infections were reported in the APPLY-PNH trial. Two patients had serious infections caused by *Pseudomonas aeruginosa*, an encapsulated bacterium: one patient in the iptacopan group had a urinary tract infection and one patient in the anti-C5 group had bacterial arthritis leading to sepsis. In the APPOINT-PNH trial, one serious adverse event of bacterial pneumonia occurred for which no causative organism was identified, and it was not suspected by the investigator to be related to iptacopan. See the Supplementary Results section for details regarding infections.

DISCUSSION

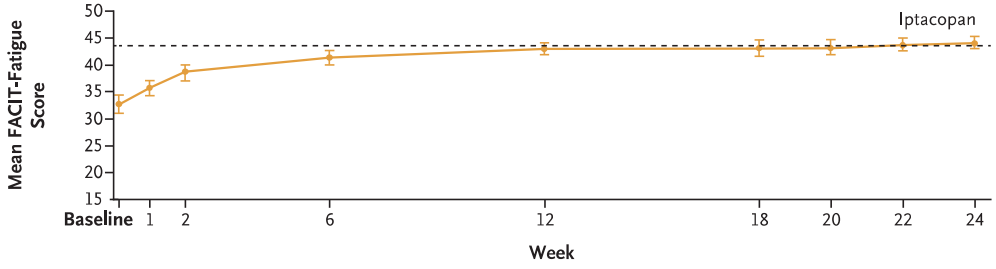
Persistent anemia due to C3-mediated extravascular hemolysis remains a risk among patients with PNH who are treated with anti-C5, with red-cell transfusions indicated in up to 40% of patients in this population.[14,31] Only 20 to 30% of patients treated with anti-C5 have been reported as having attained normal or near-normal hemoglobin levels.[14,16] Oral monotherapy with iptacopan resulted in clinically meaningful improvement in hemoglobin levels in patients with PNH who had been treated with anti-C5 and had persistent anemia and in patients who had not previously received complement inhibitor therapy. Approximately two thirds of the patients in the two trial populations attained normal or near-normal hemoglobin levels, which shows that resolution of anemia in PNH is possible with proximal complement inhibition. This hematologic response was accompanied by almost complete preclusion

A FACIT-Fatigue Scores through Week 24 in APPLY-PNH



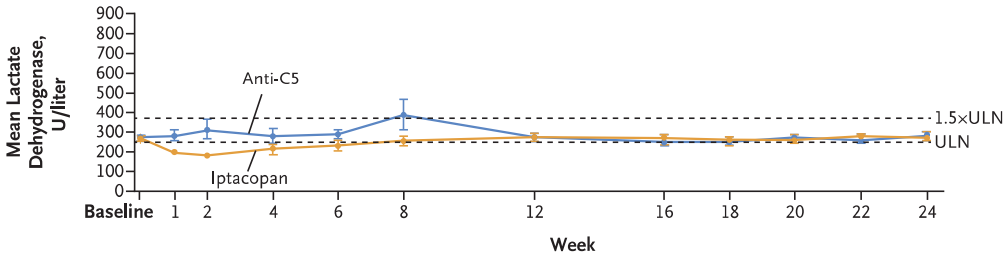
Patients with Available Data									
Iptacopan	62	60	57	61	57	58	59	56	60
Anti-C5	33	27	28	32	29	29	28	28	30

B FACIT-Fatigue Scores through Week 24 in APPOINT-PNH



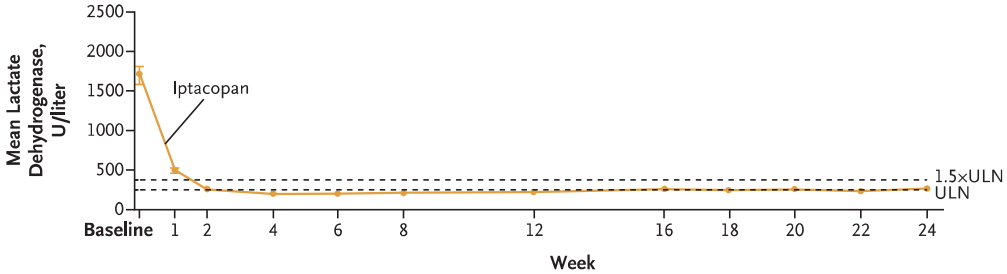
Patients with Available Data									
Iptacopan	40	36	36	39	38	35	37	36	37

C Lactate Dehydrogenase Levels through Week 24 in APPLY-PNH



Patients with Available Data												
Iptacopan	62	61	61	61	62	62	62	61	59	59	57	61
Anti-C5	35	28	28	34	34	34	34	34	35	33	32	35

D Lactate Dehydrogenase Levels through Week 24 in APPOINT-PNH



Patients with Available Data												
Iptacopan	40	40	39	39	36	37	37	31	31	35	33	39

Figure 3 (facing page). FACIT-Fatigue Scores and LDH Levels during the 24-Week Core Treatment Periods of the APPLY-PNH and APPOINT-PNH Trials.

Panel A shows the mean score on the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-Fatigue; scores range from 0 to 52, with higher scores representing less fatigue) from baseline to week 24 in the two groups in the APPLY-PNH trial. The mean FACIT-Fatigue score increased with iptacopan treatment at week 1, reached a plateau at week 6, and reached the mean score reported in a healthy general U.S. population. The mean score reported in a healthy general U.S. population, 43.6, is indicated by the dashed line in panels A and B.[32] Panel B shows the mean FACIT-Fatigue score from baseline to week 24 of the APPOINT-PNH trial. The mean FACIT-Fatigue score began to increase with iptacopan treatment at week 1, reached a plateau at week 12, and reached the mean score reported in a healthy general U.S. population. Panel C shows the mean lactate dehydrogenase (LDH) level from baseline to week 24 in the APPLY-PNH trial. The dashed lines indicate the upper limit of normal (ULN) and 1.5 times the ULN (250 U per liter and 375 U per liter, respectively). Except in week 8 in the group that received anti-C5, the mean LDH level remained below 1.5 times the ULN in both groups throughout the trial, indicating sustained control of intravascular hemolysis. The 24-week data are derived from the final data sets at trial completion. The 24-week data previously reported in congress abstracts were from interim data sets generated while the trials were ongoing (at which point the databases were still live); therefore, minor numerical differences exist between the final 24-week efficacy data reported here and the previously reported 24-week efficacy data. Panel D shows the mean LDH level from baseline to week 24 of the APPOINT-PNH trial. The LDH level decreased within the first week of the core treatment period and continued to do so until week 4, when the level began to plateau. I bars indicate standard error.

of transfusion and by clinically meaningful reduction in patient-reported fatigue; the 24-week mean FACIT-Fatigue scores that were reported in these trials were similar to those reported in a healthy general population in the United States.[32]

Consistently low LDH levels throughout both trials showed that treatment with iptacopan controlled terminal complement-mediated intravascular hemolysis, with only mild fluctuations seen in asymptomatic patients. Iptacopan also abolished C3-mediated extravascular hemolysis in patients treated with anti-C5 and did not cause extravascular hemolysis in patients who had not previously received a complement inhibitor (a finding that is supported by negligible findings of C3d+ PNH red cells), and was associated with the normalization of absolute reticulocyte counts and bilirubin levels in the patients in both trials.

Our trials had good adherence to iptacopan. Although the follow-up in these trials was relatively short, treatment with iptacopan was safe, and no adverse events led to treatment discontinuation. Mild-to-moderate headache was the most frequently reported adverse event with iptacopan in these trials; headaches at the time of initiating treatment with other complement inhibitors are well documented.[8,24,33] Infections caused by encapsulated bacteria are an increased risk during complement inhibition[34]; the few serious infectious events in both trials were not suspected by investigators to be related to iptacopan and resolved without treatment discontinuation.

Anticomplement treatment in PNH aims to prevent destruction of CD55- and CD59-deficient PNH red cells but creates an intriguing paradox: the proportion of PNH red cells increases rather than decreases. The efficacy of iptacopan was shown in patients who attained a mean total PNH red-cell population of approximately 90%. This increase in PNH red cells may expose patients to a higher risk of clinically meaningful breakthrough hemolysis, as has been observed with pegcetacoplan.[24,35-37] However, only two of the patients treated with iptacopan in the APPLY-PNH trial and none of the patients in the APPOINT-PNH trial had clinical breakthrough hemolysis, and no patients discontinued treatment with iptacopan. Breakthrough hemolysis with iptacopan appeared to occur less frequently and to a less severe degree than with pegcetacoplan,[24] a difference potentially suggesting that iptacopan has a more favorable pharmacokinetic or pharmacodynamic profile than pegcetacoplan.[22,38] Because anticomplement treatment is lifelong in PNH and complement-amplifying events can occur at any time, follow-up beyond 24 weeks is necessary to better characterize the overall risk of breakthrough hemolysis with iptacopan.

One limitation of the APPLY-PNH trial was the open-label design, which was necessary because of the different administration routes and schedules of the treatments. However, objective laboratory-based end points and protocol-defined transfusion criteria limited potential bias. A limitation of the APPOINT-PNH trial was the single-group design; however, the prespecified success criterion was based on simulations derived from hematologic summaries in the TRIUMPH (Trans-

Table 2. Adverse Events in the 24-Week Core Treatment Periods of the APPLY-PNH and APPOINT-PNH Trials.

Event	APPLY-PNH		APPOINT-PNH
	Anti-C5 therapy (N=35)	Iptacopan (N=62)	Iptacopan (N=40)
Any adverse event	28 (80)	51 (82)	37 (92)
Severity			
Mild	13 (37)	20 (32)	26 (65)
Moderate	12 (34)	28 (45)	10 (25)
Severe*	3 (9)	3 (5)	1 (2)
Events occurring in ≥4 patients in either trial†			
Headache	1 (3)	10 (16)	11 (28)
Diarrhea	2 (6)	9 (15)	3 (8)
Nasopharyngitis	2 (6)	7 (11)	0
Nausea	1 (3)	6 (10)	2 (5)
Arthralgia	1 (3)	5 (8)	0
Coronavirus disease 2019	9 (26)	5 (8)	6 (15)
Urinary tract infection	1 (3)	5 (8)	0
Abdominal pain	1 (3)	4 (6)	2 (5)
Increase in LDH level	3 (9)	4 (6)	0
Dizziness	0	4 (6)	1 (2)
Upper respiratory tract infection	3 (9)	2 (3)	5 (12)
Breakthrough hemolysis	6 (17)	2 (3)	0

* Only one patient (in the APPOINT-PNH trial) had severe adverse events of bacterial pneumonia and chest pain.
† Shown are the most frequently occurring adverse events in the iptacopan group of the APPLY-PNH trial.

fusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria)[8] and ALXN1210-301 trials,[30] and the 15% threshold was exceeded by a factor of more than five. For both trials, longer follow-up is needed to more definitively assess the effect on thromboembolic and infectious risks among patients receiving treatment with iptacopan.

Our data show that blocking the complement system proximally at the alternative pathway with monotherapy with an oral factor B inhibitor was effective and safe and did not lead to the use of additional combined terminal blockade.[39] Iptacopan resulted in a clinically meaningful increase in hemoglobin levels and reduction in fatigue and in normal or near-normal hemoglobin levels in PNH patients with persistent anemia who had been treated with anti-C5, in whom iptacopan showed superiority to anti-C5, and in patients who had not previously received complement inhibitors. Enhancing the efficiency of anticomplement agents is likely to shift the focus of PNH treatment toward the resolution of anemia.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Régis Peffault de Latour, M.D., Alexander Röth, M.D., Austin G. Kulasekararaj, M.D., Bing Han, M.D., Phillip Scheinberg, M.D., Jaroslaw P. Maciejewski, M.D., Yasutaka Ueda, M.D., Carlos M. de Castro, M.D., Eros Di Bona, M.D., Rong Fu, M.D., Li Zhang, M.D., Morag Griffin, M.B., Ch.B., Saskia M.C. Langemeijer, M.D., Jens Panse, M.D., Hubert Schrezenmeier, M.D., Wilma Barcellini, M.D., Vitor A.Q. Mauad, M.D., Philippe Schafhausen, M.D., Suzanne Tavitian, M.D., Eloise Beggiato, M.D., Lee Ping Chew, M.D., Anna Gaya, M.D., Wei-Han Huang, M.D., Jun Ho Jang, M.D., Toshio Kitawaki, Ph.D., Abdullah Kutlar, M.D., Rosario Notaro, M.D., Vinod Pullarkat, M.D., Jörg Schubert, M.D., Louis Terriou, M.D., Michihiro Uchiyama, M.D., Lily Wong Lee Lee, M.D., Eng-Soo Yap, M.D., Flore Sicre de Fontbrune, M.D., Luana Marano, M.D., Ferras Alashkar, M.D., Shreyans Gandhi, M.D., Roochi Trikha, Ph.D., Chen Yang, M.D., Hui Liu, M.D., Richard J. Kelly, Ph.D., Britta Höchsmann, M.D., Cécile Kerloeguen, M.Sc., Partha Banerjee, Ph.D., Rafael Levitch, M.D., Rakesh Kumar, M.Sc., Zhixin Wang, M.Sc., Christine Thorburn, Ph.D., Samopriyo Maitra, Ph.D., Shujie Li, Ph.D., Aurelie Verles, M.Sc., Marion Dahlke, M.D., and Antonio M. Risitano, M.D.

The authors' affiliations are as follows: the Hematology and Transplant Unit, French Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Saint-Louis Hospital (R.P.L., F.S.F.), and Université de Paris (R.P.L.), Paris, Centre Hospitalier Universitaire (CHU) de Toulouse, Institut Universitaire du Cancer de Toulouse–Oncopole, Toulouse (S.T.), and CHU Lille, Université de Lille, Lille (L.T.) — all in France; the Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University Duisburg–Essen, Essen (A.R., F.A.), the Department of Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation, University Hospital RWTH Aachen, and the Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf, Aachen (J.P.), the University of Ulm, the Institute of Transfusion Medicine and Immunogenetics, German Red Cross Blood Transfusion Service Baden–Württemberg–Hessen, and University Hospital Ulm, Ulm (H.S., B. Höchsmann), the Department of Oncology, Hematology, and Bone Marrow Transplantation, Section of Pneumology, University Medical Center Hamburg–Eppendorf, Hamburg (P. Schafhausen), and Elblandklinikum Riesa, Riesa (J.S.) — all in Germany; King's College Hospital NHS Foundation Trust (A.G.K., S.G., R.T.), the National Institute for Health and Care Research and Wellcome King's Clinical Research Facility (A.G.K.), King's College London (A.G.K.), and Novartis Pharmaceuticals (C.T.), London, and St. James's University Hospital, Leeds (M.G., R.J.K.) — all in the United Kingdom; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College, Beijing (B. Han, C.Y.), the Department of Hematology, Tianjin Medical University General Hospital (R.F., H.L.), and the Department of Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences (L.Z.), Tianjin, and China Novartis Institutes for BioMedical Research, Shanghai (Z.W., S.L.) — all in China; the Division of Hematology, Hospital A Beneficência Portuguesa, São Paulo (P. Scheinberg), and ABC Medical School, Santo André (V.A.Q.M.) — both in Brazil; the Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland (J.P.M.); Osaka University Graduate School of Medicine, Suita (Y.U.), Kyoto University Hospital, Kyoto (T.K.), and Japanese Red Cross Society Suwa Hospital, Suwa (M.U.) — all in Japan; Duke University School of Medicine and Duke Cancer Institute, Durham, NC (C.M.C.); Unità Operativa Complessa Oncoematologia, AULSS7 Pedemontana, Bassano del Grappa (E.D.B.), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (W.B.), Division of Hematology, University of Turin, Città della Salute e della Scienza, Turin (E.B.), Instituto per lo Studio, la Prevenzione e la Rete Oncologica, and Azienda Ospedaliero–Universitaria Careggi, Florence (R.N.), AORN Moscati, Avellino (L.M., A.M.R.), and University of Naples Federico II, Naples (A.M.R.) — all in Italy; Radboud University Medical Center, Nijmegen, the Netherlands (S.M.C.L.); the Hematology Unit, Department of Medicine, Hospital Umum Sarawak, Kuching (L.P.C.), and the Hematology Unit, Queen Elizabeth Hospital, Kota Kinabalu (L.W.L.L.) — both in Malaysia; Hospital Clinic of Barcelona (A.G.) and the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (R.P.L., A.G.K., M.G., W.B., S.T., L.T., F.S.F., L.M., A.M.R.) — both in Barcelona; the Department of Hematology and Oncology and the Department of Clinical Pathology, Hualien Tzu Chi Hospital, the Buddhist Tzu Chi Medical Foundation, and the Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan (W.-H.H.); the Division of Hematology–Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (J.H.J.); Medical College of Georgia, Augusta (A.K.); City of Hope Medical Center, Duarte, CA (V.P.); the Department of Laboratory Medicine, National University Hospital, Singapore (E.-S.Y.); Novartis Pharma (C.K., R.L., M.D.) and Novartis BioMedical Research (A.V.) — both in Basel, Switzerland; and Novartis Healthcare Private, Hyderabad, India (P.B., R.K., S.M.).

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