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RESEARCH

Patient-reported outcomes in patients with paroxysmal nocturnal hemoglobinuria treated with crovalimab and approved C5 inhibitors in the phase III COMMODORE 2 and 1 studies

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Abstract

Crovalimab is a next-generation C5 inhibitor (C5i) for paroxysmal nocturnal hemoglobinuria (PNH) treatment with every-4-weeks low-volume subcutaneous maintenance dosing and the possibility for self-administration. Patient-reported outcomes (PROs) with crovalimab versus other C5is were evaluated in C5i-naive and experienced adult patients in COMMODORE 2 and 1 (NCT04434092; NCT04432584; both registered June 12, 2020), respectively. For primary analyses, patients were randomized to treatment with crovalimab or eculizumab. All patients continuing in the extension period received crovalimab. During the 24-week primary treatment period, both COMMODORE 2 arms showed rapid and sustained improvement from baseline across PROs assessing fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue), other PNH symptoms (European Organisation for Research and Treatment of Cancer [EORTC] Item Library-40), and functioning and global health status/quality of life (GHS/QoL; EORTC QoL Questionnaire Core 30). In COMMODORE 1, baseline levels of PROs were maintained throughout the primary treatment period. Across studies, most patients (60–85%; including COMMODORE 1 non-randomized patients) preferred crovalimab to eculizumab or ravulizumab (Patient Preference Questionnaire), mainly driven by easier and faster administration and fewer hospital visits required. Crovalimab was rated more convenient (Treatment Satisfaction and Medication Questionnaire-9) than eculizumab across the randomized arms of both studies, with similar global satisfaction and perceived efficacy. Overall, COMMODORE 2 and 1 data on relevant aspects of health-related QoL support the treatment benefit of crovalimab from the patient perspective and show its potential as a less burdensome option than other therapies for this lifelong disease.

Keywords Complement C5 inhibitor · Crovalimab · Eculizumab · Paroxysmal nocturnal hemoglobinuria · Patient-reported outcomes · Ravulizumab

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, acquired, clonal hematologic disease that can be life-threatening in the absence of adequate treatment [1–5]. C5 inhibitors, eculizumab and ravulizumab, are the current standard of care for PNH in countries where they are available [6]. These treatments are well tolerated and effective, reducing intravascular hemolysis and improving survival outcomes [7–12]. However, treatment with eculizumab and ravulizumab requires intravenous (IV) infusions (usually in a supervised healthcare setting, with home-based treatment available in some countries) every 2 weeks and every 8 weeks, respectively, for life [7–9].

Infusions and travel to the hospital or infusion clinic can be time-consuming, disrupting daily life [13–15]. A substantial number of patients feel frustrated because of the cumulative loss of personal and professional time due to

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lengthy infusions and travel times [14]. Further, invasive IV infusions and time at the hospital can be a constant reminder of being ill and may expose patients to pathogens [14, 15]. Overall, the treatment burden of IV infusions can negatively impact work, leisure and family time, the ability to socialize and travel, and financial security due to an inability to work [14–17].

Since most patients typically present with PNH symptoms between 30 and 40 years old, the burden of IV infusions can last for decades [18]. Hence, additional therapeutic options are needed to reduce the treatment burden for patients with this lifelong disease.

Crovalimab is a next-generation novel humanized anti-C5 monoclonal antibody that is approved for the treatment of PNH [19–22]. Crovalimab was developed by leveraging Chugai's recycling antibody technology with novel surface-charge engineering, allowing for low-volume, subcutaneous maintenance dosing every 4 weeks following a loading series (IV dose on day 1 followed by subcutaneous doses) with the possibility for self-administration by patients or caregivers at home or outside of a healthcare setting [23, 24]. Crovalimab binds to a C5 epitope that is different from the one that eculizumab and ravulizumab bind to and can therefore block C5 activation in patients with a C5 single nucleotide polymorphism, unlike eculizumab and ravulizumab [7, 8, 23, 25].

The global, randomized, phase III COMMODORE 2 study in C5 inhibitor-naive patients with PNH demonstrated that crovalimab was non-inferior to eculizumab for hemolysis control, transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization, with clinically meaningful improvement in fatigue observed in both arms [26]. The safety profile of crovalimab was consistent with that of eculizumab [26].

In the global, randomized, phase III COMMODORE 1 study, crovalimab was further evaluated versus eculizumab in patients with PNH who were previously treated with a C5 inhibitor [27]. COMMODORE 1 showed that crovalimab was well tolerated, with a safety profile consistent with that in patients who were C5 inhibitor naive, except for the identified risk of transient immune complex reactions when switching between crovalimab and other C5 inhibitors, which occurred in about one in six patients [27]. Additionally, patients who switched from eculizumab to crovalimab maintained disease control and fatigue levels that were achieved previously [27].

Here, patient-reported outcomes (PROs) were evaluated in patients treated with crovalimab versus eculizumab in COMMODORE 2 and COMMODORE 1, with assessments of fatigue, other PNH symptoms, functioning, and global health status/quality of life (GHS/QoL). Patient preference and treatment satisfaction were also assessed.

Methods

Study design and patient population

Details of the two COMMODORE studies were previously published (Supplementary Figure S1) [26, 27]. The phase III, global, randomized, open-label, active controlled COMMODORE 2 (NCT04434092) study comprises two parts: (1) randomized arms investigating crovalimab versus eculizumab in complement inhibitor-naive adult patients (≥ 18 years old), and (2) a descriptive, non-randomized arm exploring crovalimab in complement inhibitor-naive pediatric patients (< 18 years old) [26]. PRO results from the non-randomized arm of COMMODORE 2 are not included in this analysis. The phase III, global, randomized, open-label, active controlled COMMODORE 1 (NCT04432584) trial consists of two parts: (1) randomized arms evaluating crovalimab versus eculizumab in adult patients with PNH who had adequately controlled intravascular hemolysis receiving approved dosing of eculizumab and (2) a descriptive, non-randomized arm evaluating crovalimab in patients with PNH <18 years old, those previously receiving ravulizumab, those previously receiving approved or higher-than-approved eculizumab dosing, and those with the C5 R885H polymorphism who had poorly controlled hemolysis with eculizumab or ravulizumab [27]. Only data from adult patients in the randomized arms of COMMODORE 1 and from patients who previously received ravulizumab are presented in this paper. Patients in both studies weighed ≥40 kg and had a documented PNH diagnosis [26, 27]. Detailed eligibility criteria are available in prior publications [26, 27].

In both studies, the primary treatment period was 24 weeks, and all patients who continued after week 25 received crovalimab [26, 27]. Patients who discontinued the study treatment at any time entered a safety follow-up period.

Protocol approval for COMMODORE 2 and 1 was obtained from the institutional review board or ethics committee at each site [26, 27]. Both studies were conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. All patients provided written informed consent to participate in the respective studies. The study sponsors supplied the study drugs and collaborated with academic authors on the study design, data collection, data analysis, and data interpretation.

Interventions

In COMMODORE 2 and 1, crovalimab was administered using a weight-based tiered dosing regimen comprising a loading series (IV dose on day 1 followed by subcutaneous injections) and maintenance dosing (every-4-weeks

subcutaneous injections) [26, 27]. Crovalimab self-administration by patient or caregiver was permitted from week 9 onwards, after training and confirmation of proficiency by a healthcare provider. Patients randomized to the eculizumab arm of COMMODORE 2 and 1 received eculizumab per local guidelines, i.e., loading doses followed by 900 mg IV maintenance dose every 2 weeks [26, 27].

Study objectives and endpoints

Study objectives and endpoints of COMMODORE 2 and 1 were previously described [26, 27]. The objective of this descriptive analysis was to evaluate PROs with crovalimab and eculizumab treatment in the randomized arms of these two studies and to assess treatment preference and satisfaction in the non-randomized arm of COMMODORE 1 (Supplementary Figure S1).

In both COMMODORE 2 and 1, patients completed paper PRO questionnaires at baseline (defined as the patient's last observation prior to initiation of study drug in the primary treatment period) and at weeks 2, 5, 9, 17, and 25 during the primary treatment period (up to week 25; Supplementary Figure S2). PRO questionnaires were administered before patients received study treatment and before they were provided any information on their disease status. Patient-reported fatigue was assessed using the 13-item Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (version 4), with higher scores indicating lower fatigue severity. Additional PNH symptoms (i.e., dyspnea, dysphagia, headaches, abdominal pain, chest pain, and erectile dysfunction) were evaluated using a curated measure of select questions from the European Organisation for Research and Treatment of Cancer Item Library-40 (i.e., EORTC IL-40). All EORTC IL-40 items were scored on a 4-point scale ranging from 'not at all' to 'very much'. Based on the EORTC scoring guidelines, these scores were transformed to a 0–100 scale, with higher scores indicating worse symptom severity [28].

Physical functioning, role functioning, and GHS/QoL were evaluated using the relevant scales from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), with higher scores indicating better functioning or QoL.

Treatment preference was assessed using the two-item Patient Preference Questionnaire that was developed and content validated by the sponsor [29]. Patients in all COMMODORE 1 arms, and patients initially randomized to eculizumab who switched to crovalimab after 24 weeks of treatment in COMMODORE 2, were asked to indicate their preference for IV eculizumab or ravulizumab (as applicable) versus subcutaneous crovalimab and to select reasons for their preference after 17 weeks of crovalimab treatment. Treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9), which includes nine items to evaluate the perceived efficacy and convenience of medication, as well as global satisfaction with medication [30, 31]. Each domain was scored on a 0–100 scale, with higher scores indicating higher satisfaction. All adult patients in COMMODORE 2 and 1 were asked to complete the TSQM-9 questionnaire at week 13 and at the end of the primary treatment period (week 25). Patients in both studies who were initially randomized to eculizumab and switched to crovalimab at week 25 were additionally requested to complete the TSQM-9 assessment after 24 weeks of crovalimab treatment in the extension period (switch week 25).

Statistical analyses

Descriptive analyses of all PROs were conducted in adult patients in the randomized primary efficacy analysis population of COMMODORE 2 and adult patients who were randomized ≥24 weeks before the clinical cutoff date in COMMODORE 1 [26,27]. In addition, analyses of treatment preference and treatment satisfaction were conducted in adult patients who were enrolled in the non-randomized arm of COMMODORE 1.

All analyses are descriptive and prespecified unless otherwise indicated. All continuous variables were summarized using descriptive statistics: *n*, mean, standard deviation, median, minimum, and maximum. The frequency and percentages (based on the non-missing sample size) of observed variables were reported for all categorical measures. Post-hoc estimates of absolute mean change from baseline to week 25 in individual FACIT-Fatigue item scores were calculated.

Results

Patients

At clinical data cutoff for the primary analysis (November 16, 2022), 204 patients (crovalimab: $n = 135$; eculizumab: $n = 69$) were randomized in COMMODORE 2 and 89 patients (crovalimab: $n = 45$; eculizumab: $n = 44$) were randomized in COMMODORE 1. A total of 21 patients who previously received ravulizumab were enrolled into COMMODORE 1. Baseline demographics and characteristics of randomized patients in COMMODORE 2 and 1 were previously reported [26, 27].

In patients who received prior ravulizumab in COMMODORE 1, the majority of patients were male (57%) and did not undergo any packed red blood cell transfusions

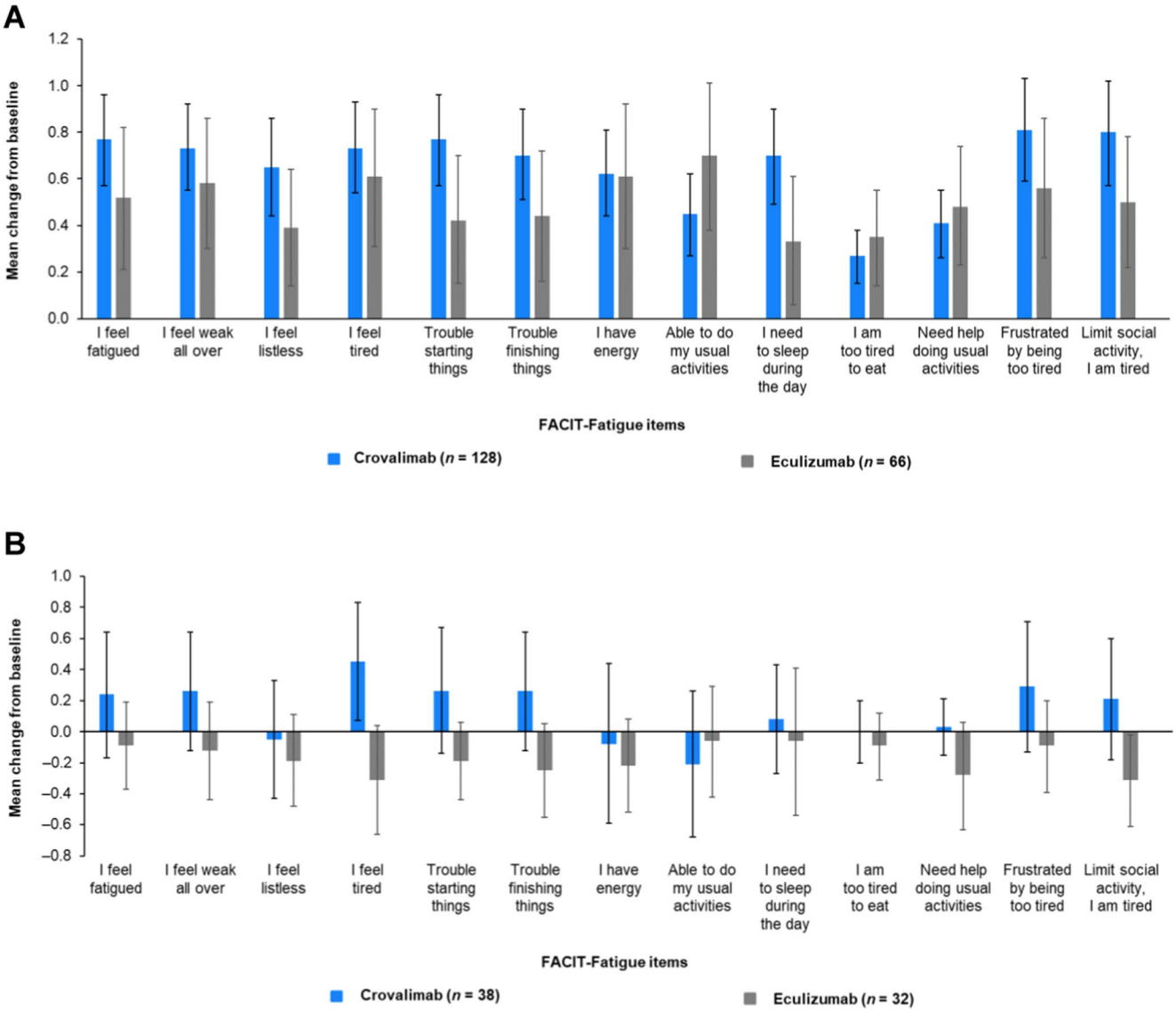

Fig. 1 Mean change from baseline to week 25 in individual FACIT-Fatigue items in (**A**) COMMODORE 2 and (**B**) COMMODORE 1. FACIT-Fatigue items presented in this figure have been reverse-scored as necessary such that positive mean changes reflect improvement. Error bars represent 95% CIs. At week 25, questionnaire completion rate in adults ≥18 years old was 99% in the crovalimab arm and 97% in the eculizumab arm of COMMODORE 2, and 97% in the crovalimab arm and 91% in the eculizumab arm of COMMODORE 1. CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy

within 12 months prior to screening (86%; Supplementary Table S1). History of aplastic anemia was present in 43% of patients.

Fatigue – FACIT-Fatigue

In COMMODORE 2, C5 inhibitor-naive patients in both arms showed clinically meaningful improvement (≥ 5 points) in FACIT-Fatigue scores from baseline to week 25, with mean fatigue levels in patients treated with crovalimab reaching normative population levels (estimated to be 43.5–46.6) by week 17 [26, 32–35]. The adjusted mean change was 7.8 in the crovalimab arm (95% confidence interval [CI]: 6.5, 9.1) and 5.2 in the eculizumab arm (95% CI: 3.4, 6.9) [26]. C5 inhibitor-experienced patients in both randomized arms of COMMODORE 1 maintained baseline levels of fatigue [27]. A post-hoc analysis of individual FACIT-Fatigue items in COMMODORE 2 showed that the range of mean change scores across items was 0.27 to 0.81 in the crovalimab arm versus 0.33 to 0.70 in the eculizumab arm. Items with the most improvement in the crovalimab arm included "I feel fatigued", "I feel listless", "trouble starting things", "trouble finishing things", "I need to sleep during the day", "frustrated by being too tired", and "limited

Table 1 Mean absolute change from baseline to week 25 in EORTC IL-40 scores

Change in EORTC IL-40 scores, mean (95% CI)	COMMODORE 2[a]		COMMODORE 1[b]	
	Crovalimab (n = 128)	Eculizumab (n = 66)	Crovalimab (n = 38)	Eculizumab (n = 32)
Dyspnea	−13.4 (− 16.9, −9.9)	−14.8 (− 19.9, −9.7)	3.2 (− 3.3, 9.7)	−0.4 (− 5.4, 4.7)
Dysphagia	−4.4 (− 7.7, −1.1)	−6.1 (− 12.1, 0.0)	0.9 (− 3.1, 4.9)	−4.2 (− 9.2, 0.9)
Headaches	−6.8 (− 11.2, −2.4)	−4.6 (− 9.1, 0.0)	−1.8 (− 9.4, 5.9)	−1.0 (− 11.4, 9.3)
Abdominal pain	−8.9 (− 12.8, −4.9)	−7.1 (− 13.7, −0.4)	−0.9 (− 7.9, 6.1)	−2.1 (− 8.9, 4.7)
Chest pain	−4.7 (− 7.7, −1.7)	−8.1 (− 13.3, −2.9)	0.0 (− 2.6, 2.6)	0.0 (− 5.3, 5.3)
Erectile dysfunction[c]	−18.0 (− 24.5, −11.4)	−10.0 (− 19.3, −0.7)	6.7 (− 14.5, 27.8)	7.1 (− 11.6, 25.9)

Negative change indicates improvement in symptoms from baseline. At week 25, questionnaire completion rate[d] in adults ≥ 18 years old was 99% for the crovalimab arm and 97% for the eculizumab arm in COMMODORE 2 and 97% and 91%, respectively, in COMMODORE 1

CI, confidence interval; *EORTC IL-40*, European Organisation for Research and Treatment of Cancer Item Library-40

[a]C5 inhibitor-naive patients

[b]C5 inhibitor-experienced patients

[c]Evaluated in male patients only. For COMMODORE 2, n = 65 for crovalimab and n= 30 for eculizumab. For COMMODORE 1, n= 15 for crovalimab and n= 14 for eculizumab

[d]Questionnaire completion rates apply to all scores except erectile dysfunction, which was assessed in male patients only

social activity, I am tired" (Fig. 1A). In COMMODORE 1, the range of mean change scores across items showed more improvement or reduced worsening with crovalimab (range, −0.21 to 0.45) than with eculizumab (range, −0.31 to −0.06), especially in "I feel tired", "trouble starting things", "need help doing usual activities", and "limited social activity, I am tired" (Fig. 1B).

PNH symptoms – EORTC IL-40

C5 inhibitor-naive patients in both randomized treatment arms of COMMODORE 2 showed a negative change in all mean EORTC IL-40 symptom scores (crovalimab: range of mean change, −4.4 to −18.0 points; eculizumab: −4.6 to −14.8 points), indicating improvement from baseline to week 25 (Table 1). In C5 inhibitor-experienced patients in COMMODORE 1, baseline symptom scores were generally maintained in both arms up to week 25 (crovalimab: range of mean change, −1.8 to 6.7; eculizumab: −4.2 to 7.1). Positive change in erectile dysfunction scores, suggesting worsening of the symptom, was observed in male patients in both the crovalimab (n= 15; mean change, 6.7 points [95% CI: −14.5, 27.8]) and eculizumab arms (n= 14; mean change, 7.1 points [95% CI: −11.6, 25.9]) of COMMODORE 1. However, due to the small sample size these results should be interpreted with caution.

Functioning and GHS/QoL – EORTC QLQ-C30

In COMMODORE 2, C5 inhibitor-naive patients in both randomized arms showed an improvement from baseline in mean scores across the physical functioning, role functioning, and GHS/QoL scales of the EORTC QLQ-C30 (crovalimab: range, 12.3 to 13.4 points; eculizumab: 9.9 to 14.2 points) at week 25, indicating an improvement from baseline. These improvements began at week 2 and were sustained during the primary treatment period (Fig. 2A) [36]. C5 inhibitor-experienced patients in COMMODORE 1 maintained baseline levels of physical functioning, role functioning, and GHS/QoL scores in both arms up to week 25 (crovalimab: range of mean change, 0.9 to 5.7 points; eculizumab: −3.7 to 0.4 points) (Fig. 2B).

Treatment preference

Amongst randomized patients in COMMODORE 2 and 1 who completed the treatment preference questionnaire after 17 weeks of crovalimab treatment, 84% in COMMODORE 2 and 85% in COMMODORE 1 preferred crovalimab to eculizumab [26, 27]. Across studies, the top reasons for crovalimab preference (up to three reasons could be selected) were "treatment required fewer hospital visits" (associated with treatment; n= 47), "treatment was easier to administer" (n= 41), "treatment took less time to administer" (n= 39), and "treatment provided a better quality of life" (n= 30) in the 92 patients who preferred crovalimab. Of the five patients who indicated a preference for eculizumab across studies, top reasons were "treatment provided a better quality of life" (n= 4), "treatment had less effect on other activities" (n= 3), "treatment allowed me to think about my disease less" (n= 2), and "I had fewer symptoms with treatment" (n= 2) [26, 27].

Treatment preference was also examined at week 17 in patients who previously received ravulizumab in COMMODORE 1. Crovalimab was preferred by 9 of 15 (60%) patients evaluated who switched from ravulizumab to crovalimab (Fig. 3). The top reasons selected for crovalimab preference in the nine ravulizumab-experienced patients were "treatment was easier to administer" (n= 6), "treatment took less time to administer" (n= 4), and "treatment

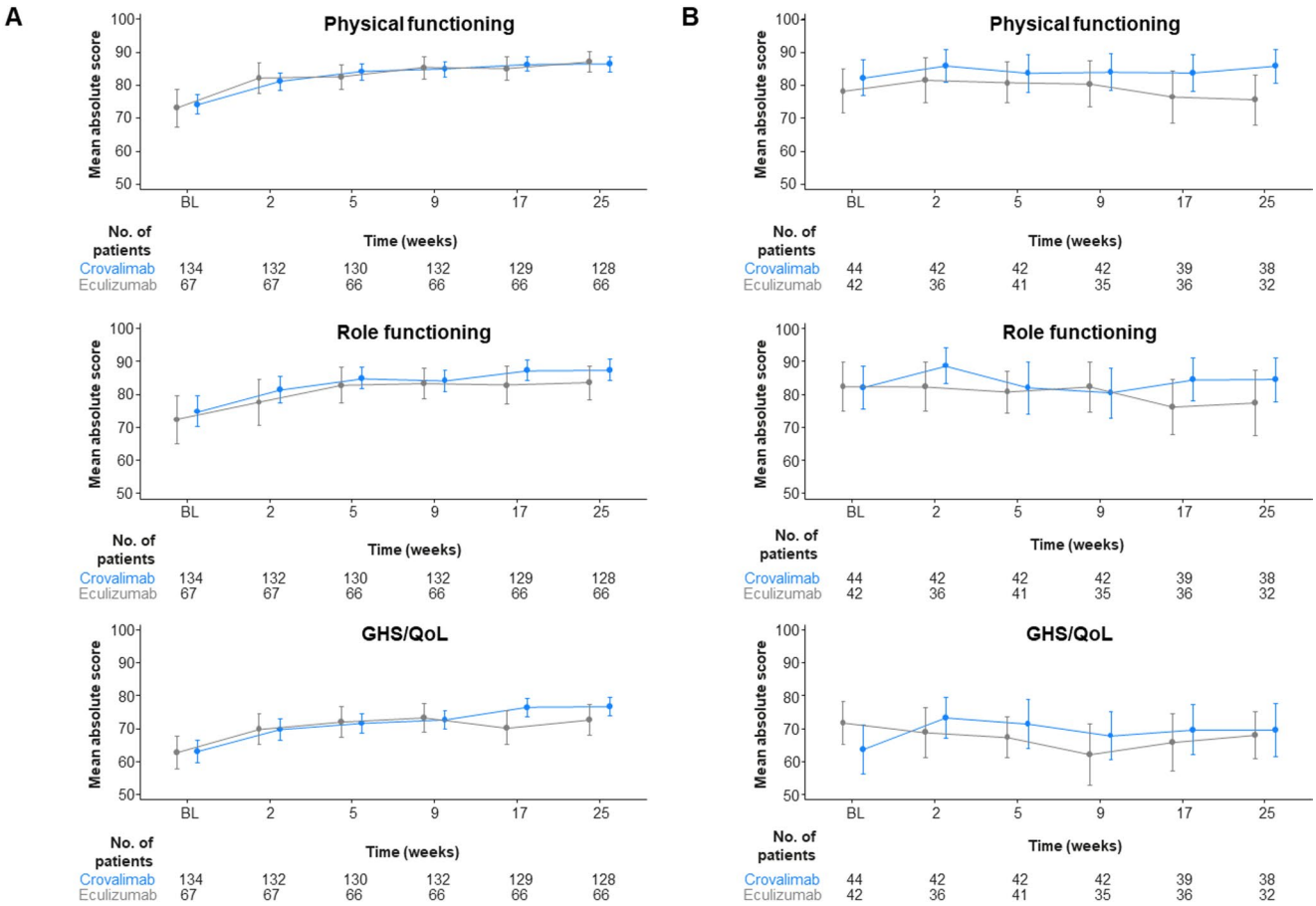

Fig. 2 Mean EORTC QLQ-C30 scores from baseline to week 25 in (**A**) C5 inhibitor-naive patients in COMMODORE 2 and (**B**) C5 inhibitor-experienced patients in COMMODORE 1. Higher scores indicate better functioning or GHS/QoL. Error bars represent 95% CIs. Questionnaire completion rate was 100% for the crovalimab arm and 97% for the eculizumab arm in COMMODORE 2 at baseline and 99% and 97%, respectively, at week 25. In COMMODORE 1, questionnaire completion rate was 100% in each randomized arm at baseline and 97% and 91% in the crovalimab and eculizumab arms, respectively, at week 25. BL, baseline; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; QoL, quality of life

provided the option to treat my disease at home" ($n = 4$). Of the four patients who indicated a preference for ravulizumab, top reasons selected were "treatment was easier to administer" ($n = 2$) and "treatment had less effect on other activities" ($n = 2$).

Treatment satisfaction – TSQM-9

At week 25 of the primary treatment period, C5 inhibitor-naive patients in both randomized treatment arms of COMMODORE 2 reported similar mean absolute TSQM-9 scores for perceived efficacy (crovalimab: 77.7 [95% CI: 74.3–81.1]; eculizumab: 77.1 [95% CI: 72.1–82.1]) and global satisfaction (crovalimab: 78.5 [95% CI: 75.5–81.4]; eculizumab: 77.8 [95% CI: 73.4–82.2]; Fig. 4A and B). Mean absolute TSQM-9 convenience scores at week 25 were higher with crovalimab (75.7 points [95% CI: 72.7–78.8]) than with eculizumab (66.2 points [95% CI: 61.2–71.3]; Fig. 4C). In COMMODORE 1, C5 inhibitor-experienced patients had comparable mean absolute TSQM-9 scores for perceived efficacy (crovalimab: 77.1 [95% CI: 70.7–83.4]; eculizumab: 73.2 [95% CI: 66.8–79.6]) and global satisfaction (crovalimab: 79.1 [95% CI: 72.9–85.4]; eculizumab: 71.0 [95% CI: 63.4–78.5]) between both arms (Fig. 4A and B) at week 25. Mean absolute TSQM-9 convenience scores at week 25 were higher with crovalimab (81.0 points [95% CI: 76.2–85.8]) than with eculizumab (60.8 points [95% CI: 52.3–69.2]) (Fig. 4C).

Among COMMODORE 2 patients who were initially randomized to eculizumab and subsequently switched to crovalimab at the end of the 24-week primary treatment period, mean absolute TSQM-9 scores were generally maintained at switch week 25 of the extension period for perceived efficacy (switch baseline: 77.4 [95% CI: 72.5–82.4]; switch week 25: 71.3 [95% CI: 64.2–78.4]) and global satisfaction (switch baseline: 78.1 [95% CI: 73.7–82.5]; switch

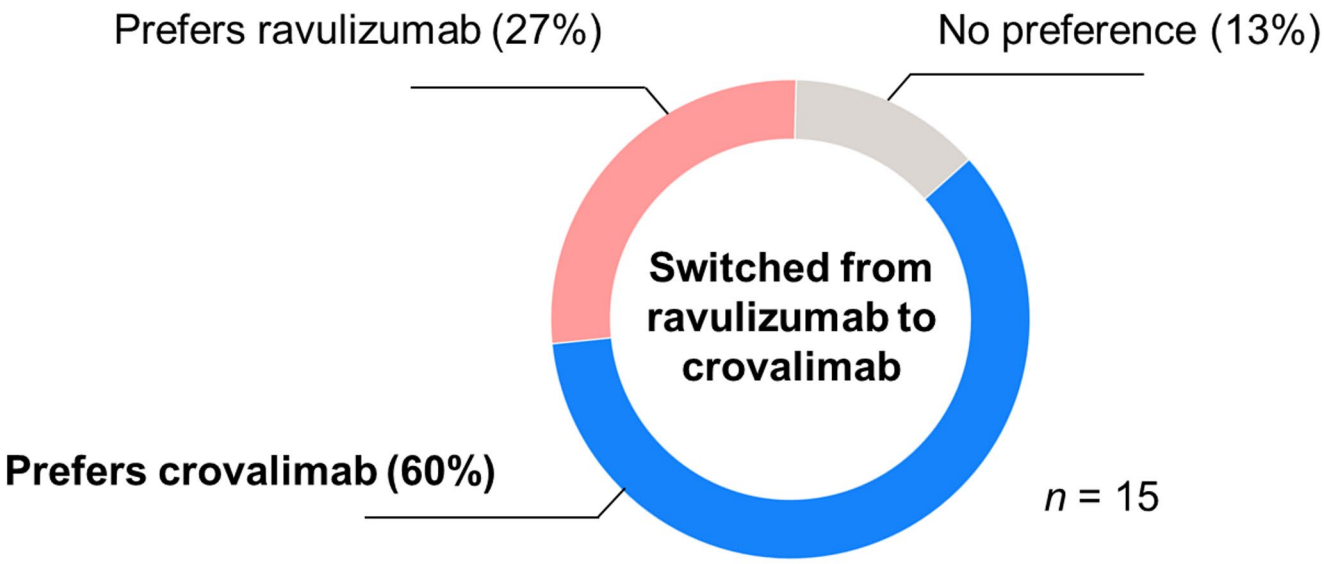

Fig. 3 Treatment preference among patients who switched from ravulizumab to crovalimab in COMMODORE 1. All patients were assessed after 17 weeks of crovalimab treatment. Only patients with available data (having completed the questionnaire) were included in the calculations of percentages. Questionnaire completion rate was 88%

week 25: 73.4 [95% CI: 66.6–80.2]; Fig. 5A and B). Mean absolute TSQM-9 convenience scores were 66.8 points (95% CI: 61.7–71.8) at switch baseline and 72.7 points (95% CI: 67.2–78.2) at switch week 25 (Fig. 5C). Similarly, in COMMODORE 1 randomized patients who switched from eculizumab to crovalimab, TSQM-9 scores for perceived efficacy (switch baseline: 69.5 [95% CI: 61.8–77.2]; switch week 25: 76.3 [95% CI: 67.8–84.8]) and global satisfaction (switch baseline: 69.6 [95% CI: 62.6–76.6]; switch week 25: 78.6 [95% CI: 72.8–85.3]) were comparable at switch baseline and at switch week 25 (Fig. 5A and B). Mean absolute TSQM-9 convenience scores were higher at switch week 25 (78.9 points [95% CI: 73.4–84.3]) than at switch baseline (60.0 points [95% CI: 52.0–68.0]) (Fig. 5C).

Mean absolute TSQM-9 efficacy, global satisfaction, and convenience scores in the prior ravulizumab subgroup of COMMODORE 1 are shown in Supplementary Table S2.

Discussion

Overall, PRO data from COMMODORE 2 and 1 support the treatment benefit of crovalimab. C5 inhibitor-naive patients in the randomized crovalimab and eculizumab arms of COMMODORE 2 experienced rapid and sustained improvements from baseline in fatigue, other PNH symptoms, physical and role functioning, and GHS/QoL scores. Baseline levels of fatigue and other PROs were maintained during the first 24 weeks of crovalimab or eculizumab treatment in C5 inhibitor-experienced patients in the randomized arms of COMMODORE 1. Most patients in COMMODORE 2 and 1 preferred treatment with crovalimab to other C5 inhibitor therapies. The preference for crovalimab to eculizumab was largely driven by increased convenience due to reduced treatment frequency as well as easier and faster mode of administration. Reasons for preferring crovalimab to ravulizumab were mainly due to the easier and faster mode of administration, and the option to treat their condition at home. Of note, in some healthcare systems, ravulizumab may be administered at home via nursing services and further investigation in a larger study population is needed to determine the treatment preference of these patients. In both studies, treatment satisfaction and perceived efficacy with crovalimab was generally similar to that with eculizumab, with crovalimab rated as more convenient. Trends in perceived efficacy and global satisfaction scores were maintained after patients in both studies switched from eculizumab to crovalimab in the extension period, with a higher convenience score reported at switch week 25 (after 24 weeks of crovalimab) than at switch baseline (before starting crovalimab) in both studies.

Recently approved oral complement inhibitors, danicopan and iptacopan, have shown improved quality of life using the FACIT-Fatigue and EORTC QLQ-C30 measures versus

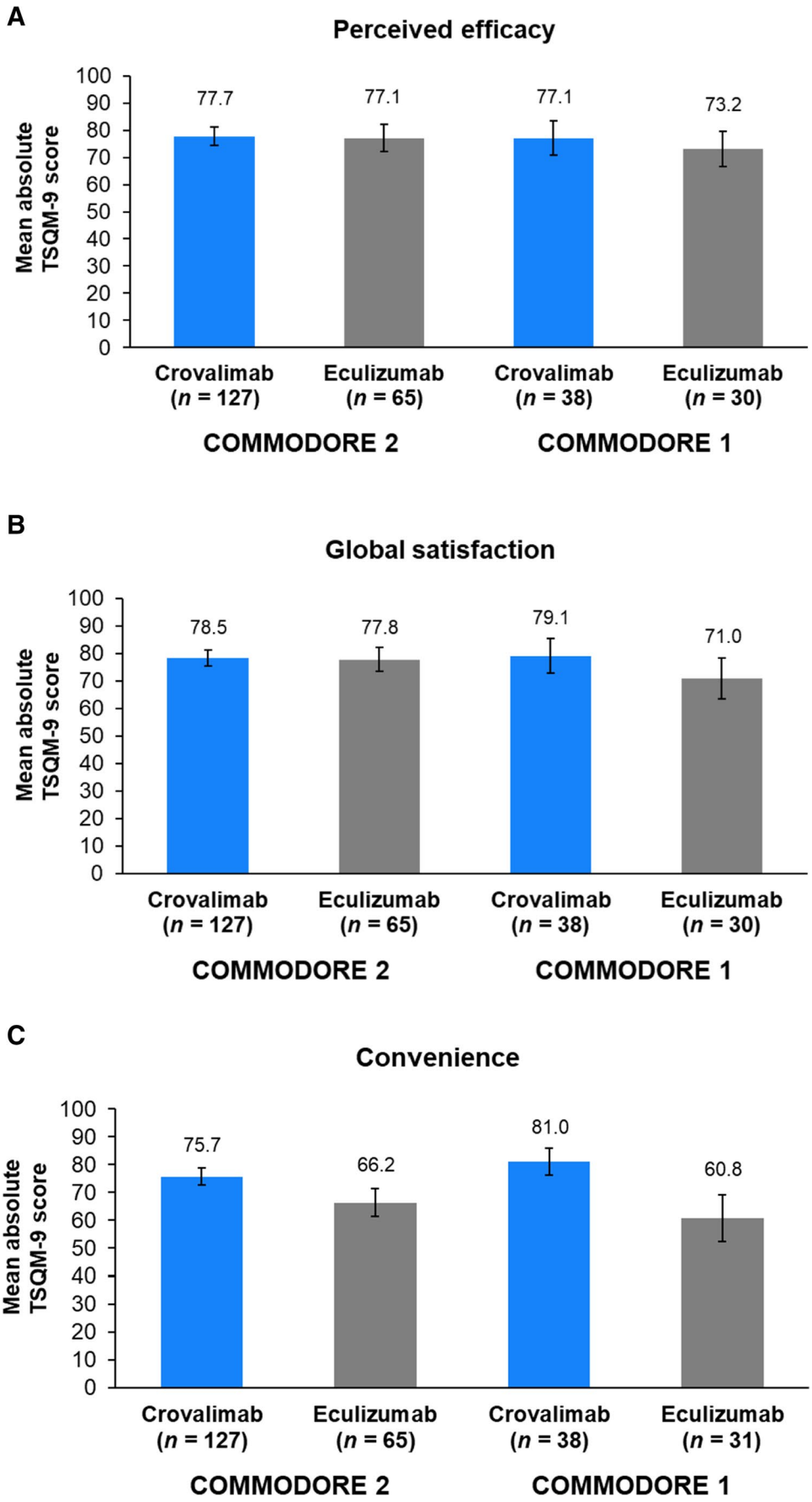

Fig. 4 Mean TSQM-9 (**A**) perceived efficacy, (**B**) global satisfaction, and (**C**) convenience scores in COMMODORE 2 and COMMODORE 1 at the end of the primary treatment period (at week 25). This questionnaire was only completed by patients ≥18 years old. Higher scores indicate better perceived efficacy, global satisfaction, or convenience. Error bars represent 95% CIs. Questionnaire completion rate was 98% for the crovalimab arm and 96% for the eculizumab arm in COMMODORE 2 and 97% for the crovalimab arm and 86–89% for the eculizumab arm in COMMODORE 1. CI, confidence interval; TSQM-9, Treatment Satisfaction Questionnaire for Medication 9

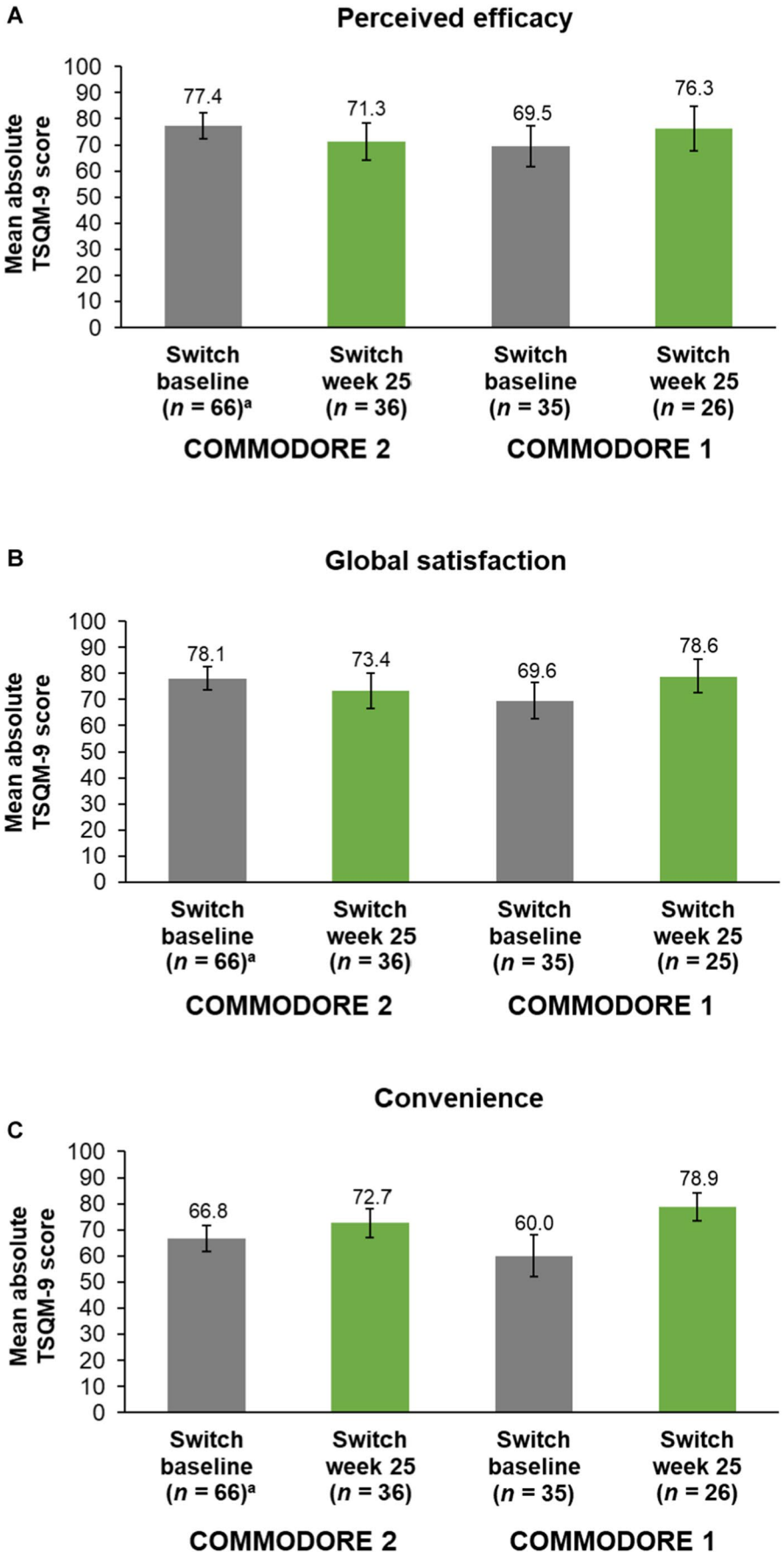

Fig. 5 Mean TSQM-9 (**A**) perceived efficacy, (**B**) global satisfaction, and (**C**) convenience scores in COMMODORE 2 and COMMODORE 1 patients randomized to eculizumab who switched to crovalimab in the extension period. This questionnaire was only completed by patients ≥18 years old. Higher scores indicate better perceived efficacy, global satisfaction, or convenience. Error bars represent 95% CIs. Switch baseline is the patient's last observation prior to initiation of crovalimab in the extension period. Switch week 25 is 24 weeks after crovalimab treatment initiation. Questionnaire completion rate was 97% at switch baseline and 90% at switch week 25 in COMMODORE 2 and 100% at switch baseline and 96–100% at switch week 25 in COMMODORE 1.[a]Two patients discontinued the study upon completing 24 weeks of eculizumab treatment. CI, confidence interval; TSQM-9, Treatment Satisfaction Questionnaire for Medication-9

IV C5 inhibitors in patients with PNH who remained anemic while receiving C5 inhibitor treatment [37, 38]. However, strict adherence to the thrice-daily dosing of danicopan and twice-daily dosing of iptacopan may present a constant challenge to patients compared with the every-4-weeks subcutaneous dosing of crovalimab. Additional studies evaluating the impact of these oral agents on QoL compared with crovalimab would aid in informing treatment decisions.

Clinically meaningful change thresholds appropriate for use in a population of patients with PNH are not currently available for some of the PROs used in this analysis. Change of ≥5 points in FACIT-Fatigue score has been indicated in PNH to represent clinically meaningful change [35]. In both randomized arms of COMMODORE 2, clinically meaningful improvements from baseline in FACIT-Fatigue score were observed [26, 27]. Although there are no established thresholds for clinically meaningful improvements in EORTC QLQ-C30 scores specific to patients with PNH, the week 25 improvements from baseline for all examined domains exceeded the thresholds that are generally accepted for cancer patients, which is a 10-point improvement across domains [39, 40]. However, thresholds are not available for other measures of PROs used in COMMODORE 2 and 1, such as EORTC IL-40 and TSQM-9, limiting the interpretation of results. Disease-specific PRO measures currently undergoing validation, such as the novel 54-item PNH-specific QLQ—AA/PNH, present potentially promising tools for standardizing the evaluation of PROs in patients with PNH in future research [41].

This analysis is limited by several factors. Primarily, all analyses were descriptive. The number of patients who received prior ravulizumab in COMMODORE 1 was small but this limitation is explained by the ultra-rare nature of PNH and that ravulizumab was recently approved when the study started [42]. Both COMMODORE 2 and 1 were open-label studies, which meant that patients were aware of the treatments they were receiving. Although knowledge of the study medicines received could affect PRO completion rates or scores and lead to reporting biases, growing evidence in other disease settings have shown that these concerns do not result in clear bias or direction of differences in PRO change scores between treatment groups in open-label versus blinded trials [43–50]. Further, high questionnaire completion rates were seen across all PRO assessments, as well as comparable baseline and change scores between randomized arms, suggesting a low likelihood of bias due to the open-label trial design [49].

Conclusions

As the available treatment options for PNH continue to grow, consideration of patient-relevant outcomes will be an important factor in treatment decisions. Data from COMMODORE 2 and 1 provide supportive evidence for the treatment benefit of crovalimab on symptoms, functioning, and GHS/QoL from the patient perspective. In addition, the majority of patients in both studies preferred treatment with crovalimab to other C5 inhibitor therapies. With subcutaneous injections every 4 weeks and the possibility for self-administration at home or outside of a supervised healthcare setting, crovalimab is a next-generation C5 inhibitor that can potentially be less burdensome than other therapies for the lifelong treatment of PNH.

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Author contributions Conceptualization: BGData curation: BG, JS, ACCFormal analysis: BG, JS, MU, ACCInvestigation: JP, BH, JC, FAGF, AG, AGK, OK, FS, PS, HS, NS, YU, and ARMethodology: BG, JS, MUValidation: BG, JS, MU, ACCVisualization: BG, JS, MU, ACCWriting - original draft preparation: BGWriting - review and editing: JP, BH, JC, FAGF, AG, AGK, OK, FS, PS, HS, NS, YU, ACC, BG, JS, MU, and AR.

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Data availability For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

Declarations

Competing interests JP is a consultant for Amgen, Apellis Pharmaceuticals Inc., Bristol Myers Squibb, MSD, and Sanofi Ltd; participated in speakers' bureaus for Alexion, Boehringer Ingelheim, Blueprint Medicines, F. Hoffmann-La Roche Ltd, Novartis, Pfizer, Samsung Bioepis, and Sobi; and is a member on the Board of Directors or advisory committee of Alexion, Boehringer Ingelheim, Blueprint Medicines, F. Hoffmann-La Roche Ltd, Novartis, Omeros, Samsung Bioepis, and Sobi. BH received honoraria from AstraZeneca, F. Hoffmann-La Roche Ltd, and Novartis; and research funding from F. Hoffmann-La Roche Ltd and Novartis. FAGF is a consultant for Alexion AstraZeneca Rare Disease, F. Hoffmann-La Roche Ltd, Novartis, and Sobi; received honoraria from Alexion AstraZeneca Rare Disease, F. Hoffmann-La Roche Ltd, Novartis, and Sobi; and participated in speakers' bureaus for Alexion AstraZeneca Rare Disease, F. Hoffmann-La Roche Ltd, Novartis, and Sobi. AG is a consultant for Alexion, Asahi Kasei, Chugai, and PharmaEssentia Japan; received honoraria from AbbVie, Alexion, AstraZeneca, Asahi Kasei, Bris-

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